CHAPTER 6

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Metabolic and Endocrine Abnormalities

INTRODUCTION

Biologic Functions of Bone. Although orthopaedists tend to focus on the role of bone as the structural support for the body, bone also plays a crucial role in maintaining serum mineral homeostasis. The serum levels of calcium and phosphorus need to be maintained under tight control, to allow for normal function of a variety of cells. The cancellous bone has a tremendously large surface area that allows for the rapid transfer of minerals stored in the bone, such as calcium, to the serum. This process occurs at over a million sites in the human skeleton, mediated by osteoblast and osteoclast cells. A variety of endocrine, metabolic, and cellular factors are crucial to maintain this tight homeostatic balance. Not only do these various factors maintain serum minerals at their proper level, but they also act to regulate the amount of bone present. The interrelationship between these metabolic and endocrine factors with the distribution of minerals between the bone and serum results in metabolic and endocrine disorders altering the quantity and quality of bone. This same interrelationship occasionally results in disorders altering bone structure dysregulating serum mineral balance (1).

Growing Bone. The effect of metabolic and endocrine disorders on the skeleton is very different in children than in adults. This is because many endocrine and metabolic factors have an effect on the growth plate. Chondrocytes in the growth plate go through a coordinated process of differentiation, beginning with a proliferative phase at the epiphyseal side of the growth plate and progressing to terminal differentiation and apoptotic cell death at the metaphyseal side of the physis. Terminal differentiation is associated with the expression of Type X collagen and the formation of scaffolding for bone formation. Blood vessels located adjacent to the physis in the metaphyseal bone bring pluripotential mesenchymal cells to the region, which differentiate into osteoblasts, producing new bone on the scaffolding left behind by the growth plate chondrocytes. This coordinated differentiation process results in longitudinal growth of long bones. The process of growth plate chondrocyte differentiation needs to be tightly regulated, since if chondrocytes on one side of the body go though this process at a different rate than growth plate chondrocytes on the other side of the body, a limb length inequality would result. The process of growth plate chondrocyte maturation is regulated by both local and systemic factors (2). Conditions in which these systemic factors are dysregulated, as is the case in several endocrinopathies, there is an associated growth plate abnormality (3). In addition, some endocrine factors that regulate bone mineral homeostasis, such as thyroid hormone, also regulate the growth plate chondrocytes. Thus, while thyroid hormone dysregulation has implications in bone density in adults, in growing children, thyroid hormone dysregulation also can cause an abnormality in the growth plate.

FACTORS THAT REGULATE BONE DENSITY

Cells. Bone density is regulated by osteoblast, osteocyte, and osteoclast cells that add to or break down bone. These cells are regulated by local and systemic factors, some of which can be modulated by the mechanical environment. All of these factors are interrelated, in a complex way that is still not completely elucidated.

Osteoblasts. Osteoblasts are the main cells responsible for lying down of new bone in the form of osteoid. These cells are

derived from pluripotential stromal precursor cells (sometimes called mesenchymal stem cells) and are the active cells that lay down new bone during skeletal growth and remodeling. Mesenchymal stem cells are very similar too and likely arise from the pericytes or perivascular cells present just deep to the endothelium of blood vessels. A very active area of basic science and translational research is harnessing the regenerative potential of mesenchymal stem cells to treat a variety of diseases (4–6). As the bone matures, osteoblasts become encased in the new bone. They produce alkaline phosphatase, an enzyme that is often used to identify osteoblasts and osteoblastic activity. Once they become encased in osteoid, they become relatively quiescent and are termed osteocytes. In mature bone, osteocytes are located extremely far away from neighboring cells, and communicate with other cells through long cytoplasmic processes. The osteocytes remain quiescent until stimulated by hormonal or mechanical factors to begin to reabsorb or lay down bone. Although osteoblasts and osteocytes are thought of as cells responsible for building new bone, they also are able to rapidly reabsorb small quantities of bone. They are able to do this in a relatively rapid manner, in contrast to osteoclasts, which require cellular differentiation and recruitment to reabsorb bone. Thus, they are the first cells that the body activates when bone reabsorption is required (7).

Osteoclasts. Osteoclasts are derived from circulating monocytes. After differentiation and recruitment to the site of bone where required, osteoclasts are able to reabsorb bone in a very robust manner. They form a ruffled boarder that attaches to the osteoid, in which proteins that degrade the bone matrix are secreted. As such, osteolasts form active reabsorption cavities called Howship lacunae. There is an intimate relationship between osteocyte and osteoclast activities, and many of the signals to activate osteoclasts are mediated by osteocytes. For instance, PTH does not directly regulate osteoclast activity but conveys information via osteocytes, which produce secondary factors that regulate the differentiation of monocytes to osteoclasts. The major signaling pathway that is used by osteocytes to regulate osteoclasts involves a member of the tumor necrosis factor superfamily called RANKL, its receptor, RANK, and a circulating inhibitor, osteoprotegerin (OPG). The receptor, RANK, is present on osteoclast precursor cells, and when stimulated, it causes these precursors to differentiate into active osteoclasts. RANKL is produced by osteocytes that are stimulated to reabsorb bone. OPG also binds to RANKL, but inhibits its ability to activate RANK, and thus inactivates osteoclasts. The balance between OPG and RANKL regulates the number of osteoclasts available (Fig. 6-1) (7, 8). Since OPG inhibits osteoclast production, its use is a promising approach to inhibiting osteoclastic activity, and as such, it has the potential to be developed into useful therapy for osteoporosis, neoplastic bone loss, and even loosening surrounding total joint implants (9, 10). Denosumab, another RANKL inhibitor, has been used in clinical trials to decrease bone turnover and increase bone mineral density (BMD) in postmenopausal females but has not yet been described for clinical use in children (11).

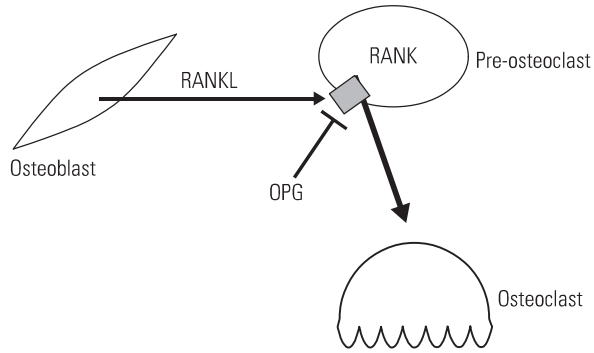


FIGURE 6-1. Expression of RANKL by osteoblasts and osteocytes activates RANK receptor on preosteoclasts to cause differentiation into active osteoclasts. OPG is a circulating factor that can also bind to RANK, but inhibits its ability to cause differentiation to osteoclasts.

Genetic Mechanisms Controlling Bone Density. In recent years, there have been tremendous advances made into understanding genes that regulate how these cells develop. Much of this information is covered in several review articles (1, 2) and is beyond the scope of this textbook. For the purpose of this chapter, we consider three modulators of bone density: physical forces, hormone factors, and calcium homeostasis.

Hierarchy in the Regulation of Bone Mass. There is a hierarchy among the various factors regulating bone mass. Calcium mobilization overrides the other functions of the skeleton. Calcium deficiency due to renal disease, malabsorption, or poor calcium diet invariably causes bone loss, which cannot be overcome by modulating any of the other factors that regulate bone mass. Hormone effects, such as that of estrogen, seem to be more potent than the effect of physical forces. This is suggested by the fact that exercise is limited in its ability to maintain or restore bone mass in postmenopausal women and amenorrhoeic marathon runners lose bone. Of the three modulators of bone mass—calcium availability, hormonal, and physical forces—the last has the least pronounced effects, although this is the one that orthopaedic surgery concentrates most of its efforts on (7).

Calcium Homeostasis

Biologic Functions of Calcium. Calcium plays a crucial role in the irritability, conductivity, and contractility of smooth and skeletal muscle, and the irritability and conductivity of nerves. Small changes in extracellular and intracellular calcium levels lead to dysfunction of these cells. For the case of neurons, the cellular activity is inversely proportional to the calcium ion concentration, while for cardiac myocytes there is a direct proportionality. Thus, decreases in ionic calcium concentration can lead to tetany, convulsions, or diastolic death. Conversely, increases in the concentration of calcium can lead to muscle weakness, somnolence, and ventricular fibrillation. It is obviously important for the body to guard the concentration of ionized calcium, thus providing a rationale for the overriding importance of calcium homeostasis in modulating bone density (12, 13).

Normal Calcium Balance. Calcium is absorbed from the gut, stored in bone, and excreted primarily by the kidney. Thus, diseases that effect gut absorption or renal function have the potential to deregulate normal calcium homeostasis, and bone mass. In addition, some conditions that cause massive loss of bone mass, such as widespread metastatic disease or prolonged bed rest, also can alter serum calcium levels. Almost all of the body's calcium is stored in the bones and is held in the form of hydroxyapatite, a salt that is composed of calcium, phosphorus, hydrogen, and oxygen $Ca_{10}(PO_4)_6(OH)_2$ in very tiny crystals embedded in the collagen fibers of the cortical and cancellous bone (14–17). The small size of the crystals provides an enormous surface area, and this factor, combined with the reactivity of the crystal surface and the hydration shell that surrounds it, allows a rapid exchange process with the extracellular fluid (ECF). This process converts the mechanically solid structure of bone to a highly interactive reservoir for calcium, phosphorus, and a number of other ions (16, 18).

Serum Calcium and Phosphate Naturally Crystallizes. Hydroxyapatite is not freely soluble in water. At the pH of body fluids, calcium and phosphate concentrations in the serum exceed the critical solubility product, and are predicted to precipitate into a solid form. It is thought that various plasma proteins act to inhibit the precipitation, and keep these ions in solution. This metastable state is important for bone structure, as it allows the deposition of hydroxyapatite during bone formation with a minimal expenditure of energy. Unfortunately, it also makes ectopic calcification and ossification easy to occur as a result of increments in levels of either or both of these ions.

Active Transport of Calcium Regulators. Calcium cannot passively diffuse across mammalian cell membranes, and as such, requires an active transport machinery to move into or out of cells (12, 16, 18–20). Although the mechanism to control this transport is regulated in a large part by the action of the active form of vitamin D, parathyroid hormone (PTH), and the concentration of phosphate (18, 21, 22), a variety of other cell signaling pathways also play a role in calcium transport across cell membranes. These other cell signaling pathways, however, seem to act in specialized cell types under specific physiologic states, and as such, likely play only a small role regulating the total serum calcium level. As such, PTH, vitamin D, and phosphate are the three factors that play the most crucial roles in the calcium transport process, and thus in maintaining the normal extracellular soluble calcium level.

Parathyroid Hormone. PTH is produced by cells of the parathyroid glands, and the expression level of PTH is regulated by the serum level of ionized calcium. When serum calcium levels are low, there is an increase in PTH expression, protein production, and ultimately increased PTH levels in the serum. There are four parathyroid glands, and any one gland has the potential to produce enough PTH to maintain calcium homeostasis. This is of importance in the surgical management of thyroid neoplasia, in which it is preferable to maintain the viability of at least one parathyroid gland. PTH binds to a family of cell membrane receptors (parathyroid hormone receptors, PTHR), which activate a number of cell signaling pathways. The pathway studied most in the control of calcium is one that regulates adenyl cyclase activity, resulting in an increased cellular level of cyclic adenosine monophosphate (cAMP). cAMP renders the cell membrane more permeable to ionic calcium, and it induces the mitochondria, which are intracellular storehouses for calcium, to release their calcium. These actions increase the intracellular concentration of calcium, but do not promote transport to the extracellular space, a function that also requires vitamin D. PTH acts with 1,25-dihydroxyvitamin D to facilitate cellular calcium transport in the gut, the renal tubule, and in the lysis of hydroxyapatite crystal (20, 21, 23). PTH directly stimulates osteoblasts to begin to degrade the surrounding calcium-rich osteoid. Osteoclasts do not contain receptors for PTH, but are stimulated by PTH activation in osteoblasts through induction of the expression of RANKL, which activates osteoclasts (23, 24). Another action of PTH is to diminish the tubular reabsorption of phosphate, which causes the renal excretion of phosphate (23, 25, 26).

Vitamin D. Active vitamin D is produced from provitamins through conversion steps in the skin, liver, and kidney (Fig. 6-2). The provitamins are ingested in animal fats (ergosterol) or synthesized by the liver (7-dehydrocholesterol) (14, 20, 27) and are converted to calciferol and cholecalciferol by ultraviolet light, a process that occurs in the skin. In the absence of ultraviolet light, this conversion cannot occur, explaining the vitamin D deficiency associated with prolonged periods indoors away from ultraviolet light sources, such as in chronically ill individuals, or in people living in extremely cold climates (14, 28). The compounds are then transported to the liver, where they are converted to 25-hydroxyvitamin D by a specific hydrolase (29–33). Severe liver disease or drugs that block hydrolase activity will inhibit the production of 25-hydroxyvitamin D, also potentially leading to vitamin D deficiency. The final conversion occurs in the kidney. In the presence of specific hydrolases and a number of biochemical cofactors. 25-hydroxyvitamin D is converted to either 24,25-dihydroxyvitamin D or 1,25-dihydroxyvitamin D. The latter serves as the potent calcium transport promoter (34–36). A low serum calcium level and a high PTH level cause conversion to the 1,25 analog, while a high serum calcium level, a higher serum phosphate level, and a low PTH level favor formation of 24,25-dihydroxyvitamin D, which is less potent in activating calcium transport (Fig. 6-3) (34, 37–40). Serum phosphate also plays an important role here, as a high concentration of phosphate shunts the 25-hydroxyvitamin D into the 24,25-dihydroxy form. Although the 24,25-dihydroxy form is less active in its effects regulating calcium, it has an important role in growth plate chondrocytes. This crucial role for conversion of vitamin D in the kidney, as well as the kidney's important role excreting excess calcium and phosphorus, explains the particularly deleterious effect of renal failure on bone homeostasis, causing

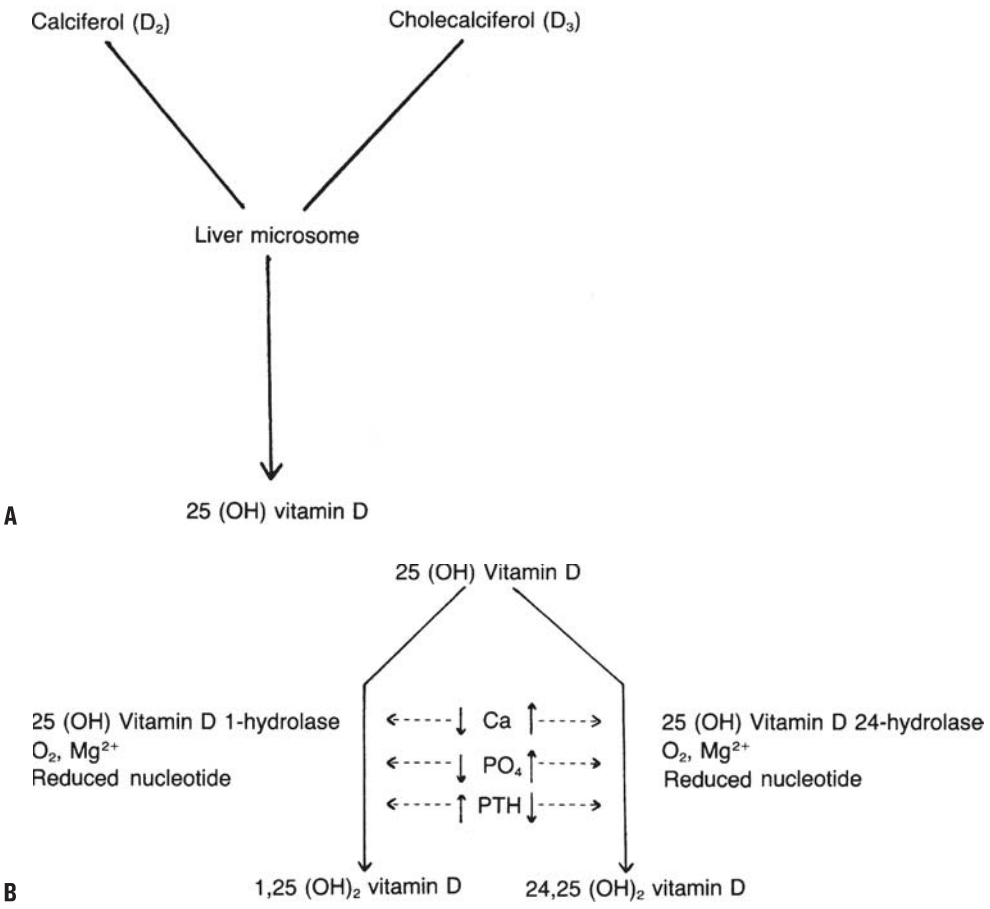


FIGURE 6-2. The conversion of vitamin D from the skin or from dietary sources takes place in the liver and kidney. **A:** In the liver, the enzyme vitamin D 25-hydrolase acts to form 25-hydroxy vitamin D. **B:** The second conversion of vitamin D takes place in the kidney, where at least two pathways have been described. The *maintenance* pathway (when the need is minimal, as defined by a normal calcium and phosphorus and low PTH level) occurs in the presence of a specific enzyme (25-hydroxyvitamin D 24-hydrolase) and results in the less active 24,25-dihydroxyvitamin D. If calcium transport is required, as signaled by the presence of low serum calcium and phosphorus levels and a high PTH level, the body converts the 25-hydroxyvitamine D to the much more active form, 1,25-dihydroxyvitamin D.

vitamin D deficiency as well as directly deregulating normal calcium excretion. Because of the crucial role of vitamin D in calcium metabolism, the National Academy of Sciences and the American Academy of Pediatrics recommend 200 IU per day of vitamin D (41). This dose will prevent physical signs of vitamin D deficiency and maintain serum 25-hydroxyvitamin D at or above 27.5 nmol/L (11 ng/mL). Many professional bodies and experts are currently advocating for increased intake of vitamin D for healthy children, with credible recommendations ranging from 400 to 1000 IU (42, 43). The generic name of 1,25-dihydroxyvitamin D is calcitriol. Recent studies found that vitamin D also has a variety of extraskeletal effects, including modulating the immune response, and as a chemoprotective agent against certain cancers (42–44).

Dietary Calcium Intake. Dietary calcium is crucial to the maintenance of bone mass. Daily requirements vary with the need of calcium during periods of rapid bone growth. Recommendations from the American Academy of Pediatrics are summarized in Table 6-1 (12, 28, 45, 46). Adequate calcium in the diet during adolescent years is important in the maintenance of bone mass over the long-term, and the orthopaedist should counsel their patients about the importance of appropriate amounts of calcium, as well as vitamin D, in their diet. Several dietary factors alter calcium absorption. Calcium salts are more soluble in acid media, and loss of the normal contribution of acid from the stomach reduces the solubility of the calcium salts and decreases the absorption of the ionized cation. A diet rich in phosphate may decrease the absorption of calcium by binding the cation to HPO_4^{2-} and precipitating most of the ingested calcium as insoluble material (16, 47). Ionic calcium can be chelated by some organic materials with a high affinity for the element, such as phytate, oxalate, and citrate. Although these materials may remain soluble, they cannot be absorbed (16, 47–49). Calcium, in the presence of a free fatty acid, forms an insoluble soap that cannot be absorbed (47, 50). Disorders of the biliary or enteric tracts, associated with steatorrhea, are likely to reduce the absorption of calcium, because it forms an insoluble compound, and because ingested fat-soluble vitamin D is less likely to be absorbed under these circumstances (51).

Dietary Phosphate Intake. Phosphate (PO_4) is absorbed lower in the gastrointestinal tract than calcium and is freely transported across the gut cell to enter the extracellular space, in which it represents a major buffer system. Transport into and out of the bone is passive and related to the kinetics of the formation and breakdown of hydroxyapatite crystals. Tubular reabsorption of phosphate, however, is highly variable, with reabsorption ranging from almost 100% to <50%. The principal factor in decreasing tubular reabsorption of phosphate is *PTH*.

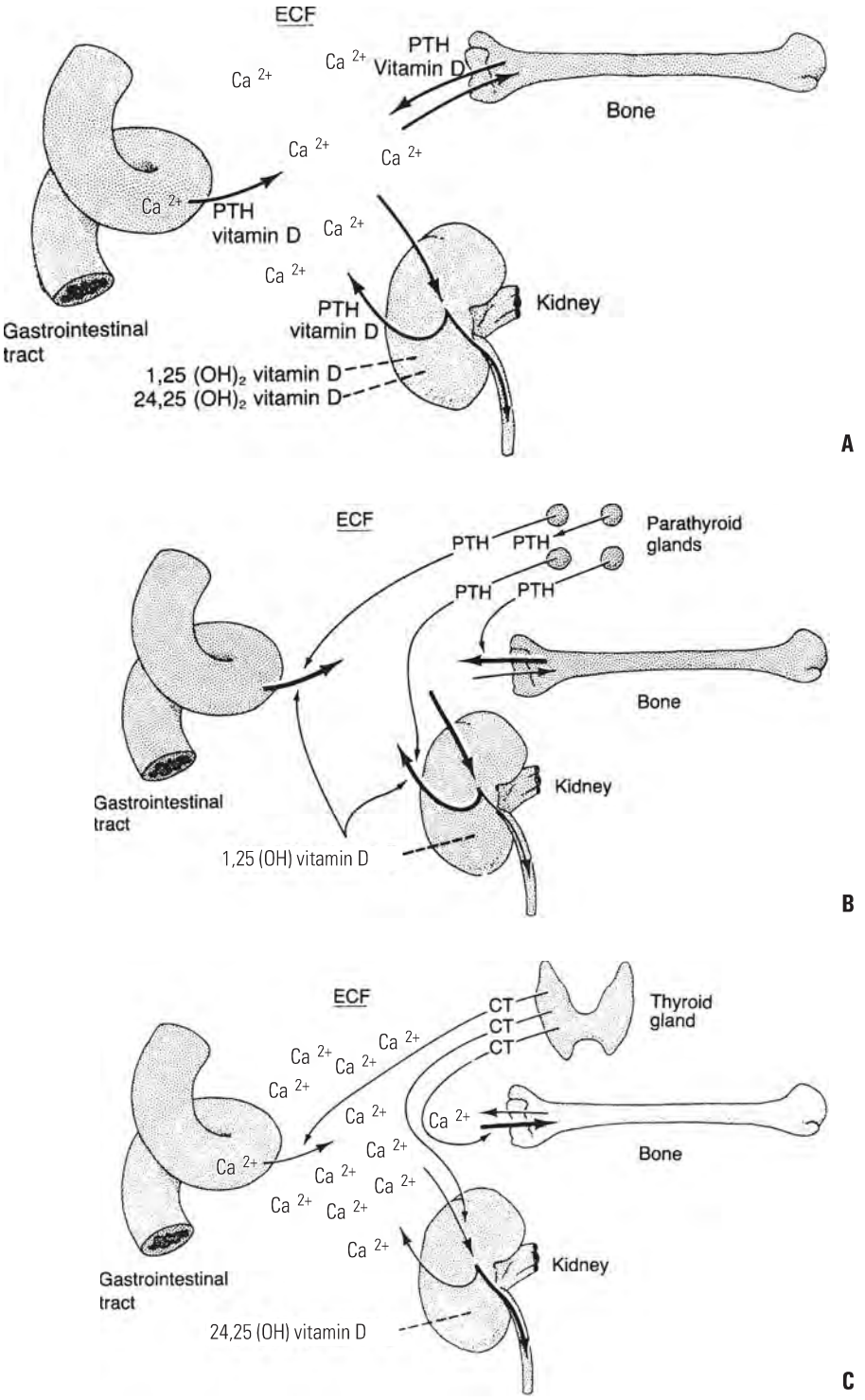


FIGURE 6-3. The roles of the bone, kidneys, gastrointestinal tract, parathyroid gland, and thyroid gland in calcium kinetics. These organs act to maintain calcium in the ECF at the appropriate levels for normal cellular function. **A:** Vitamin D and PTH act to transport calcium ions across the gut wall and regulate renal excretion and, thereby, bone calcium content. Depending on the need for increased transport, 25-hydroxy vitamin D is converted to 24,25- or 1,25-dihydroxyvitamin D. **B:** In the normocalcemic state, a reduced concentration of calcium signals the parathyroid glands to release more PTH, which acts at the levels of the gut cell, renal tubule, and bone to increase transport of calcium and rapidly replenish body fluids with it. An increase in PTH also favors the synthesis of 1,25-dihydroxvitamin D in the kidney and acts to promote renal phosphate excretion by markedly diminishing the tubular reabsorption of phosphate. **C:** In the hypercalcemic state, low concentrations of calcium and PTH act independently to diminish the synthesis of 1,25-dihydroxyvitamin D and decrease transport of calcium in the gut cell, tubule, and bone. Increased concentrations of calcium also cause the release of CT from the C cells of the thyroid gland, thereby diminishing calcium concentration. This mechanism principally involves stabilizing the osteoclast and decreasing its action on the bone, but it is not very effective in humans.

Endocrine Factors

Sex Steroids. The most potent endocrine regulator of bone density is estrogen. Much of the clinical and experimental data on the role of estrogen in bone have been generated from data on postmenopausal women. However, clinical data from children with deficiencies in sex hormones, such as in Turner syndrome, show that a lack of estrogen in growing girls also is responsible for profound loss of bone density. The exact mechanism by which estrogen regulates bone formation and loss is unknown. Estrogen receptors are present on both osteoblasts and osteoclasts, yet the cellular mechanism by which estrogen alters these cells' behavior is not clear. Studies in animals suggest that estrogen exhibits at least some of its effects through the regulation of pluripotential stromal cells in the bone marrow, a process which may be mediated by interleukin-6. Estrogen also suppresses the activation of osteoclasts by inhibiting the activation of RANK in the precursor cells (52, 53).

Androgens also seem to regulate bone mass, although the mechanism is less well understood than for estrogen. Idiopathic hypogonadotropic hypogonadism is associated

TABLE 6-1 Dietary Calcium Requirements

Age	Calcium Requirement (mg/d)
0 to 6 mo	210
6 mo to 1 y	270
1 through 3 y	500
4 through 8 y	800
9 through 18 y	1300

with decreased bone mass, and there is an association between delayed puberty and low bone mass in boys, suggesting a positive role for androgens regulating bone mass (54).

Thyroid Hormones. Thyroid hormones act in the cell nucleus, interacting with nuclear proteins and DNA to increase the expression of a variety of genes, ultimately positively regulating cell activity. As such, thyroid hormone activates both osteoblasts and osteoclasts. The actual effect on bone mass depends on the body's balance between these two cell types and how well the normal control of calcium level is able to counteract the heightened activity of these cell types. In general, the balance is in favor of the osteoclast, and most often increased thyroid hormone levels result in bone loss (55, 56).

Corticosteroids. Corticosteroids have a variety of effects on cells. They inhibit cellular activity in general, potentially decreasing the ability of osteoblasts to lay down new bone. They also have profound effects on the skeleton based on their effect on calcium regulation in the kidney, where they increase calcium excretion. This leads secondarily to elevated PTH levels, with its negative effects on bone density (57, 58).

Calcitonin. Calcitonin (CT) is produced by parafollicular thyroid cells. Although CT causes inhibition of bone resorbtion by osteoclasts and osteoblasts and decreases reabsorption of calcium and phosphate in the kidneys in animal models and cell cultures, it seems to play little role in humans (59, 60).

Mechanical Factors. Excessive reductions in bone strain produced by weightlessness (microgravity in outer space) or immobilization (paralysis, prolonged bed rest, or application of casts) can cause significant bone loss, while strenuous athletic activity can augment certain bones (60, 61). This effect is important in the pediatric orthopaedic population, in which many of the neuromuscular disorders are associated with decreased weight bearing and associated osteoporosis. Bone remodels according to the mechanical stresses applied, a phenomenon termed Wolff law. It is well known that mechanical environment alters cell behavior and gene expression, and it is thought that such a mechanism, most likely acting through osteocytes, is responsible for the effect of weight bearing on bone density as well as for the changes attributable to Wolff's law (62, 63).

FACTORS THAT REGULATE GROWTH PLATE CHONDROCYTES

In recent years, a number of signaling pathways that regulate the function of growth plate chondrocytes have been elucidated (2). General information about growth plate development and its local regulation is covered in the chapter on developmental biology. However, it is apparent that the growth plate chondrocytes are affected either primarily or secondarily by a variety of endocrine regulatory factors, and as such, a short review here is warranted. Growth plate chondrocytes at the epiphyseal side of the growth plate reside in the resting zone. They begin to proliferate and as such advance toward the metaphyseal side of the growth plate in the proliferative zone. Following this, they enter a prehypertrophic zone, where they shift from proliferation to differentiation. It is also in this prehypertrophic zone that important signals that regulate the differentiation process such as PTH-related protein and Indian hedgehog are present. Following this, the cells hypertrophy form columns in the hypertrophic zone, and then undergo terminal differentiation and cell death. Blood vessels from the metaphysis are present adjacent to the terminally differentiated chondrocytes, bringing in new pluripotential mesenchymal cells, which will differentiate into osteoblasts, forming the new bone on the scaffolding left behind by the chondrocytes. This last region is sometimes called the zone of provisional calcification.

It is easy to imagine how hormones can tip the balance in favor of or against the differentiation process in these cells. In addition, agents that alter normal bone formation by osteoblasts can also alter the growth plate, by preventing the normal replacement of the terminally differentiating chondrocytes with new bone. This inhibition of normal ossification results in the characteristic growth plate changes in rickets, in which there is an increased zone of terminal differentiation. Endocrinopathies can also alter the size and matrix components in the various zones of the growth plate. Such disorders effect terminal differentiation and may make the growth plate mechanically weaker in this region, predisposing to conditions such as slipped capital femoral epiphysis. In a similar manner, it may make the growth plate chondrocytes easier to deform with compressive pressure, causing deformities such as genu varum. This explains the high frequency of these growth plate deformities in children with endocrine disorders. Like in bone, mechanical factors can also play a role in growth pate function. The Hueter-Volkmann principle states that growth plates exhibit increased growth in response to tension and decreased growth in response to compression (64). Thus, an endocrinopathy can cause growth plate deformities, which can then be exacerbated by the effect of the changing mechanical axis in the effected limb.

Similar to the situation in bone, there is also a hierarchal regulation of the growth plate, with endocrine factors playing a dominant role over mechanical factors (3, 65). This is readily apparent in conditions such as rickets, where surgery will not result in correction of genu varum in the absence of correction of the underlying endocrinopathy in the growing child. Thus, it is important to avoid the temptation for surgical correction

of a deformity in a growing child with an endocrine disorder until the endocrinopathy is also treated.

There are a large number of endocrine factors that play a role regulating growth plate function. In many cases, not much is known about the intracellular signaling mechanisms utilized by these factors. Growth hormone plays an important role regulating growth plate chondrocytes proliferation, mediated by somatomedins. In an absence of growth hormone, there is a slowing of growth plate maturation, as well as a slowing of the rate of long bone growth. Thyroid hormone also plays a role regulating chondrocyte activity, by increasing the metabolic and proliferative rate of the growth plate chondrocytes. PTH may alter growth pate chondrocyte maturation, as the PTH receptor, PTHR1 is expressed in prehypertrophic chondrocytes, and its stimulation results in an inhibition of terminal differentiation. Nutrition and insulin also regulate growth plate chondrocytes, in a similar manner to growth hormone, by regulating growth plate chondrocyte proliferation. A lack of dietary protein exerts a negative control over the somatomedins. Excess glucocorticoids also inhibit growth, partly by an inhibitory effect on protein synthesis in cartilage, but also by interference with somatomedin production and action (3). Although these factors all play roles regulating growth plate chondrocytes, in the coming years we will likely learn more about the role of such factors in a variety of growth plate pathologies, including disorders such as slipped capital femoral epiphysis, where it is well known that a variety of endocrinopathies are predisposing conditions.

DISEASES OF BONE

Rickets

Context/Common Features. Rickets describes the clinical condition of inadequate mineralization of growing bone. Severe nutritional rickets was endemic in early industrialized societies particularly where sunlight was scarce. Accordingly, severe rachitic deformities were commonly seen in the early days of orthopaedics (66, 67). In developed countries, nutritional rickets is now a rarity, although it may present *de novo* to pediatric orthopaedists for diagnosis. Inherited form of rickets remain commonly seen in the United States (68). The surgeon should also be familiar with renal tubular abnormalities, which can result in rickets, as well as with the clinical entity of renal osteodystrophy, which describes the bone disease associated with end-stage renal disease and includes features of rickets as well as secondary hyperparathyroidism.

The clinical manifestations of all forms of rickets are similar and, therefore, clinical presentation will be covered separately prior to breaking down the various etiologies.

Clinical Presentation. Rickets is failure or delay of calcification of newly formed bone at long bone physes. The manifestations include changes in the growth plate morphology with decreased longitudinal growth and angular deformities of the long bones. Osteomalacia, which is failure of mineralization of osteoid formed at cortical and trabecular surfaces, often accompanies rickets in childhood. Osteomalacia is the only result in the adult of the mechanisms, which cause rickets in childhood.

The skeletal abnormalities of severe rickets present in early childhood and often before the age of 2 years. The child may have a history consistent with hypocalcemia in infancy including apneic spells, convulsions, tetany, and stridor prior to age of 6 months (69). The child is often hypotonic with delayed motor milestones for sitting, crawling, and walking. There is proximal muscle weakness and sometimes perfuse sweating. Cardiomyopathy and respiratory and gastrointestinal infections can accompany the clinical presentation (70–75).

Skeletal deformities can be evident at every physis. The wrists, elbows, and knees are thickened, and the long bones are short. Genu varum or valgum may be present. Coxa vara may be present. Costochondral enlargement leads to the characteristic rachitic rosary appearance of the chest. Harrison sulcus is an indentation of the lower ribs caused by indrawing against the soft bone. Kyphoscoliosis can be present. Closure of the anterior fontanelle is delayed. Frontal and parietal bossing of the skull is evident. Plagiocephaly may be related to positioning on a soft skull. Delayed primary dentition is common (68, 76).

Radiographic Changes. The radiographic hallmark of rickets is widened and indistinct growth plates (Fig. 6-4). In a normal child, the distance between the metaphysis and epiphysis of the distal radius should never be >1 mm (77).

Lateral expansion of the growth plates also occurs, particularly with weight bearing. Crawling children weight bear on their wrists, explaining the thickened wrists as well as knees. The metaphysis typically takes on a cupped and splayed appearance. The long bones are short for age. The long bones show evidence of the coxa vara, genu varum, or valgum described above in the clinical deformities. Further evidence of osteomalacia radiographically may also be present. The hallmark is Looser zones. These are transverse bands of unmineralised osteoid, which typically appear in the medial aspect of the proximal femur and at the posterior aspect of the ribs. These are described as pseudofractures and often have an osteosclerotic reaction around them. In an adult, they can progress to true fractures. Acetabular protrusion and pathologic fractures complete the radiographic signs of rickets (70, 76–78).

Overview of Classification of Rickets. Bone is mineralized by the crystallization of calcium and phosphate in the presence of alkaline phosphatase enzyme. Calcium and phosphate are maintained in the body very close to their solubility coefficient by complex series of inhibitors. The control mechanisms in the physiologic state are discussed in sections above.

A useful way of thinking about rickets is to consider those conditions that reduce the availability of calcium, those conditions that reduce the availability of phosphate, and the rare condition that reduces the availability of alkaline phosphatase at the osteoblast–bone junction (Table 6-2). Nutritional rickets and end-organ insensitivity to calcitriol are problems on the calcium side. X-linked hypophosphatemia is the most common form of rickets seen today in the United States and

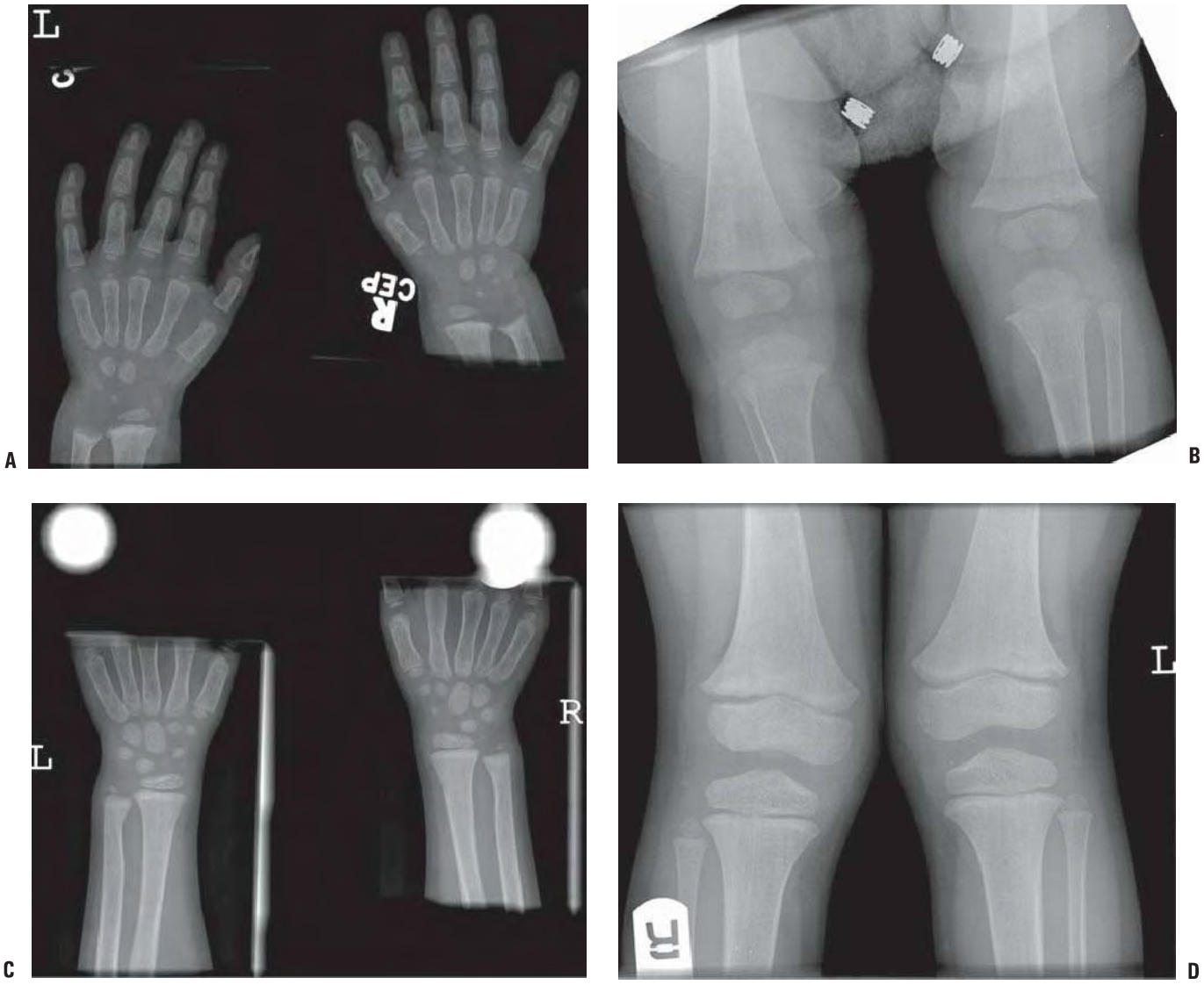


FIGURE 6-4. Rickets. Changes caused by rickets can be seen **(A)** at the wrist and **(B)** at the knees of this 1-year-old child with X-linked hypophosphatemia. The growth plates are widened and the metaphyses are cupped, particularly at the ulna and femur. At 4 years of age **(C,D)**, the changes have resolved with medical treatment.

is caused by renal tubular phosphate wasting in isolation (79). Renal tubular abnormalities including Fanconi syndrome feature renal wasting of phosphate, calcium, magnesium, and bicarbonate. Alkaline phosphatase is deficient only in one rare recessive condition, appropriately called hypophosphatasia.

Finally, renal osteodystrophy is often discussed with rickets and appropriately so since many children with renal osteodystrophy manifest findings of rickets. However, renal osteodystrophy classically includes changes of secondary hyperparathyroidism as well as those of rickets.

Nutritional Rickets. Nutritional rickets had near universal prevalence in Northern industrialized societies in the 19th century. It has now largely disappeared in developed countries. It remains a significant clinical problem in the developing world with, for example, a 66% prevalence of clinical rickets in preschool children in Tibet in 2001 (80).

The main cause of nutritional rickets is vitamin D deficiency. Vitamin D_3 (Cholecalciferol) can be produced in the skin by a process that requires ultraviolet B (UVB) radiation, or it can be ingested in the diet. Peak age of presentation of nutritional rickets is between 3 and 18 months in children who have inadequate exposure to sunlight and no vitamin D supplementation in the diet (81–83). Breast milk is poor in vitamin D and prolonged breast-feeding is a risk factor (84, 85). Vitamin D is supplemented in dairy foods in North America and diets deficient in dairy foods are therefore a risk factor (85–87). Two hundred international units of vitamin D per day is the recommended dietary amount for preventing rickets (41, 68, 68). Increasing amounts are now being recommended for optimization of bone health, with the Canadian Paediatric Society recommending 800 IU per day for northern children and the AAP recommending 400 IU per day (42). Some experts advocate 1000 IU of vitamin D per

TABLE 6-2 Classification of Rickets According to What Is Lacking at the Osteoblast-Bone Interface

Calcium
- Nutritional rickets
  - Vitamin D deficiency (common)
  - Isolated calcium deficiency (rare)
  - Combined calcium deficiency and marginal vitamin D intake (common)
- Gastrointestinal rickets
- 1α hydroxylase deficiency
- End organ insensitivity to vitamin D
- Rickets of end-stage renal disease (renal osteodystrophy)

Phosphorus
- X-linked hypophosphatemia (common)
- Renal tubular abnormalities

Alkaline Phosphatase
- Hypophosphatasia

day for all healthy children and adults (43). Sunlight exposure also prevents rickets. Two hours per week of summer sunshine at the latitude of Cincinnati (39 degrees North) is sufficient to produce adequate vitamin D in the skin. However, during the winter months in Edmonton (52 degrees North), there is insufficient UVB exposure to allow for adequate intrinsic production of vitamin D (68). A recent national survey in Canada estimated a prevalence of vitamin D deficiency rickets of at least 3 per 100,000 children, with a higher risk among breast-fed children and those dwelling in the north (88).

Although vitamin D deficiency is the principal cause of nutritional rickets, it is possible to have rickets from a profoundly calcium-deficient diet even in the presence of adequate vitamin D intake (89). Probably much more common is a subtle combination of calcium deficiency and vitamin D deficiency interacting to produce dietary rickets (90). This has been described among the modern Asian population in the United Kingdom (91, 92) and black populations in the United States (68). A diet that is low in calcium and high in phytate, oxalate, or citrate (substances found in almost all fresh and cooked vegetables and that bind calcium) means that calcium intake is poor. Vegetarians, especially those who avoid dairy products, are particularly at risk. This produces an increase in PTH that in turn increases vitamin D catabolism. Vitamin D status may have been marginal due to low sun exposure and poor dietary intake. The increased catabolism of vitamin D with marginal intake results in a vitamin D deficiency and a clinical presentation of rickets. This combination or relative deficiencies of both calcium and vitamin D together has a high prevalence among adolescents presenting with rickets in the United Kingdom and the United States.

Treatment of nutritional rickets involves adequate provision of vitamin D. The treatment dose of 5000 to 10,000 international units per day for 4 to 8 weeks should be provided along with calcium to 500 to 1000 mg per day in the diet (93). Where daily dosing and compliance were a problem, much larger doses of vitamin D (200,000 to 600,000 IU orally or intramuscularly) have given as single doses with good results (94).

Laboratory abnormalities in established nutritional rickets can include a low normal or decreased calcium ion concentration, a low serum phosphate, a low serum 25-hydroxyvitamin D_3, and a high alkaline phosphate. Alkaline phosphate drops to normal in response to successful therapy.

Gastrointestinal Rickets. Even if adequate calcium and vitamin D are present in the diet, some gastrointestinal diseases prevent its appropriate absorption (95). Gluten-sensitive enteropathy, Crohn disease, ulcerative colitis, sarcoidosis, short-gut syndromes have been implicated. If liver disease interferes with the production of bile salts, then fat accumulates in the GI tract and prevents the absorption of fat-soluble vitamins including vitamin D. The vitamin D and calcium deficiency cause bone disease in the same way as nutritional deficiencies, but the treatments are aimed at the underlying gastrointestinal problem as well as at supplementing the missing vitamin and mineral.

X-Linked Hypophosphatemia. X-linked hypophosphatemia is the most common inherited etiology for rickets with a prevalence of 1 in 20, 000 persons (96). It is an x-linked dominant disorder. This means a female-to-male patient ratio is approximately 2:1, and no male-to-male transmission. Approximately one-third of cases are sporadic (96). People with sporadic occurrence do transmit the defect to their offspring. The defect is in a gene called PHEX (79). This gene product indirectly regulates renal phosphate's transport. The defect at the kidney is isolated renal phosphate wasting leading to hypophosphatemia. In addition, a low or normal kidney production of 1,25-dihydroxyvitamin D_3 is observed, and this would be inappropriate in the hypophosphatemic state.

The clinical presentation includes rickets and mild short stature (97, 98). Dental abscesses occur in childhood, even prior to the development of dental carries (99). Adults with the condition have osteomalacia accompanied by degenerative joint disease, enthesopathies, dental abscesses, and short stature (100–102). Specific treatment for the condition is oral administration of phosphate as well as the active form of vitamin D_3, calcitriol, which is 1 alpha-hydroxylated. Treatment requires careful metabolic monitoring. Hyperparathyroidism, soft-tissue calcification, and death due to vitamin D intoxication have been problems with medical therapy in the past. Calcitriol can be used in much lower doses than the less active vitamin D metabolites previously used and are thought to be a safer therapy (79, 103, 104). Angular deformities, particularly genu valgum, may persist after medical treatment and require osteotomy (105–107). Although good initial corrections are obtained with standard techniques including external fixators, Petje reported a 90% recurrence of deformity after the first surgery and a 60% recurrence of deformity after the second surgery due to ongoing disease activity (108).

A small number of those patients with McCune-Albright syndrome also develop hypophosphatemic rickets. This syndrome includes patients with café au lait spots, precocious puberty, and fibrous dysplasia of multiple long bones. This syndrome is caused by constitutional activation of the cyclic AMP-PKA signaling pathway related to genetic defects in G signaling proteins (109).

1 Alpha-Hydroxylase Deficiency. In 1961, Prader described what was initially called vitamin D–dependent rickets (110). This was because the initial patients were treated with very large doses of vitamin D. It turns out that these patients have 1 alpha-hydroxylase deficiency and they can be treated with much smaller quantities of the biologically active 1 alpha-hydroxylated calcitriol (111). Typically, the patients present <24 weeks of age with weakness, pneumonia, seizures, bone pain, and the skeletal bone changes of rickets. Serum findings include low calcium and phosphorus, high alkaline phosphatase, and PTH with a normal level of 25-hydroxyvitamin D_3, but a markedly decreased level of 1,25-dihydroxyvitamin D_3. The patients are not able to convert the accumulated 25-hydroxyvitamin D_3 to its biologically active form of 1,25-dihydroxyvitamin D_3 and, therefore, develop clinical rickets. The autosomal recessive genetic pattern has been described (112), and the specific mutations were initially described in 1997 (113) since which time at least 31 distinct mutations in the 1 alpha-hydroxylase gene have been identified (111).

Current treatment is oral provision of activated vitamin D_3, which is curative.

End-Organ Insensitivity. In 1978, Marx (114) described two sisters with clinical rickets. The unusual clinical feature was an exceedingly high circulating level of 1,25-dihydroxyvitamin D_3. Levels can be 3 to 30 fold higher than normal (115). A striking clinical finding is alopecia or near total loss of hair from the head and the body. These patients have an end-organ insensitivity to vitamin D_3 (115). Treatment with very high doses of vitamin D produces a variable but incomplete clinical response. Intravenous high doses of calcium followed by oral calcium supplementation in large quantities have also been tried, but as yet, this rare form of rickets cannot be completely treated medically (111).

Renal Tubular Abnormalities. There is a large group of causes of the Fanconi syndrome. This syndrome implies failure of tubular reabsorption of many small molecules <50 Da. The kidneys lose phosphate, calcium, magnesium, bicarbonate, sodium, potassium, glucose, uric acid, and small amino acids. With this renal tubular abnormality, there are multiple mechanisms by which bone mineral homeostasis is disrupted (95, 116). As a result, these patients are short with rickets and delayed bone age. The predominant cause of bone disease is hypophosphatemia from renal phosphate wasting, very similar to that seen in x-linked hypophosphatemic rickets. Other mechanisms include calcium and magnesium loss, the metabolic acidosis caused by bicarbonate loss, renal osteodystrophy if renal disease is sufficient that less 1,25-dihydroxyvitamin D_3 is produced, and finally decreased calcium and phosphate reabsorption.

Treatment is similar to that of x-linked hypophosphatemia with provision of oral phosphate and vitamin D. Electrolyte imbalances from other causes need monitoring and treatment, and the underlying renal disease can also be treated if possible.

Hypophosphatasia. This is another disease with clinical overlap with rickets. Hypophosphatasia is caused by alkaline phosphatase deficiency. Like most enzyme deficiencies, this is a recessive condition with over 112 mutations described in the alkaline phosphatase gene in chromosome 1 (117–119). Clinically, alkaline phosphatase deficiency produces abnormal mineralization of bone with a presentation of rickets in the child or osteomalacia in the adult (120). Pathologic fractures can occur in children and in adults (121, 122). This is accompanied by abnormal formation of dental cementum that causes loss of teeth. The primary teeth are lost early and with minimal root resorption (123). Additional clinical manifestation can include failure to thrive, increased intercranial pressure, and craniosynostosis.

Hypophosphatasia has an estimated prevalence of 1 per 100,000 people (124). There is a perinatal lethal form. A childhood form presents with rickets at 2 or 3 years of age and remission of the disease in adolescence. An adult form presents with mild osteomalacia with pathologic fractures (117).

There is no satisfactory medical treatment of the underlying defect. Bone marrow transplantation has been used experimentally in severe cases, with the aim of repopulating the bone marrow with osteoblasts capable of producing alkaline phosphatase (117). Surgical treatment of femoral fractures and pseudofractures in the adult has been reported, with rodding techniques superior to plating techniques in the abnormal bone (121).

Renal Osteodystrophy. Renal osteodystrophy describes the bony changes accompanying end stage renal disease and is commonly seen in patients on dialysis. The clinical presentation includes hyperparathyroidism as well as rickets/osteomalacia in varying combinations (125–128).

Renal failure means inadequate clearance of phosphate from the blood once the renal function drops below 25% to 30% of normal. The hyperphosphatemia drives the solubility equilibrium to produce hypocalcemia. This hypocalcemia signals the parathyroid glands to produce PTH, causing secondary hyperparathyroidism. The bony changes of hyperparathyroidism then become evident. These include subperiosteal erosions and brown tumors (Fig. 6-5). The subperiosteal erosions are described as classically appearing on the radial margins of the middle phalanges of digit 2 and digit 3 in adults. In children, they can also be seen at the lateral aspects of the distal radius and ulna and at the medial aspect of the proximal tibia (Fig. 6-6) (129). Prolonged stimulation of the parathyroid glands can produce sufficient hyperplasia that the glands

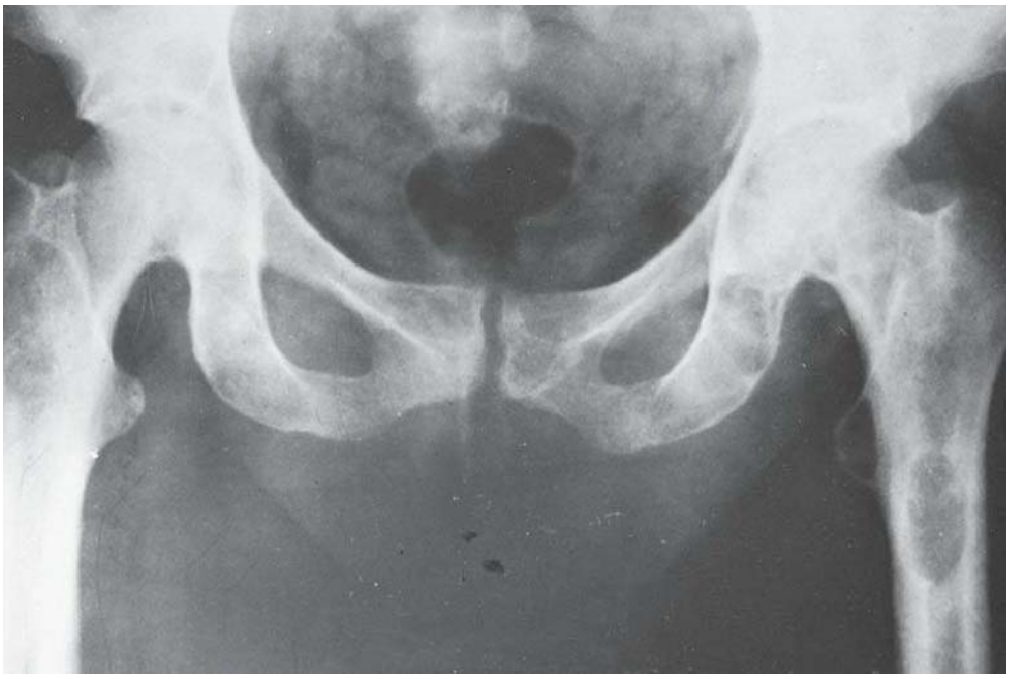


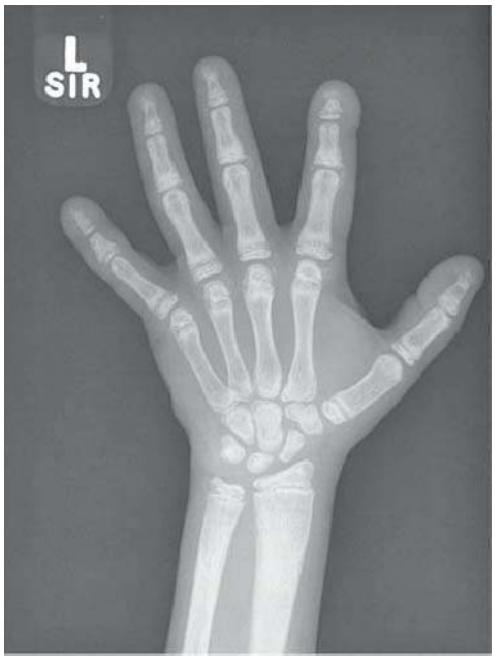
FIGURE 6-5. Radiograph of the pelvis of a patient with renal osteodystrophy shows the marked changes of secondary hyperparathyroidism. Several brown tumors are seen in the femoral shafts and ischial rami. These appear as expanded destructive lesions, resembling primary or metastatic bone tumors.

remain autonomous and maintain a hyperparathyroid state even if the end stage renal disease is treated by transplantation. In this case, the ongoing hyperparathyroidism is described as tertiary rather than secondary.

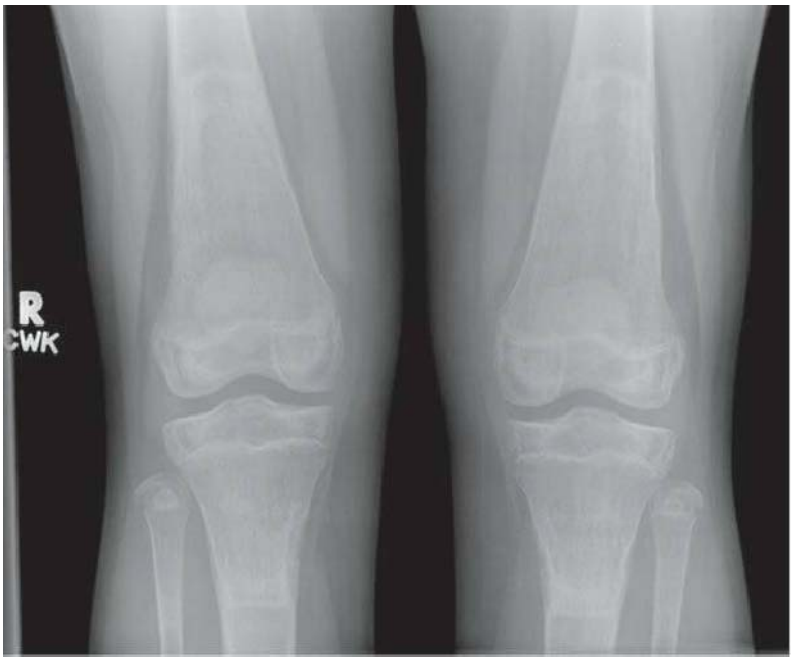
The other aspect of renal osteodystrophy is rickets. If there is inadequate renal mass to produce sufficient 1,25-dihydroxyvitamin D_3, rickets (clinical and radiographic) will accompany renal osteodystrophy. The clinical manifestations can include varus or valgus deformities at the knees or ankles, with widened and deformed growth plates radiographically, and other radiographic signs of rickets/osteomalacia such as Looser zones (Fig. 6-7).

Treatment of renal osteodystrophy includes

- Dietary phosphate restriction
- Phosphate binding agents, especially those that contain calcium



A



B

FIGURE 6-6. Renal osteodystrophy in an 8-year-old boy. **A:** Radiographs of the hand show sclerosis, acroosteolysis, and soft-tissue calcification around the metacarpal phalangeal and proximal interphalangeal joints. **B:** Radiographs of the knees show subperiosteal resorption at the medial border of the proximal tibia.

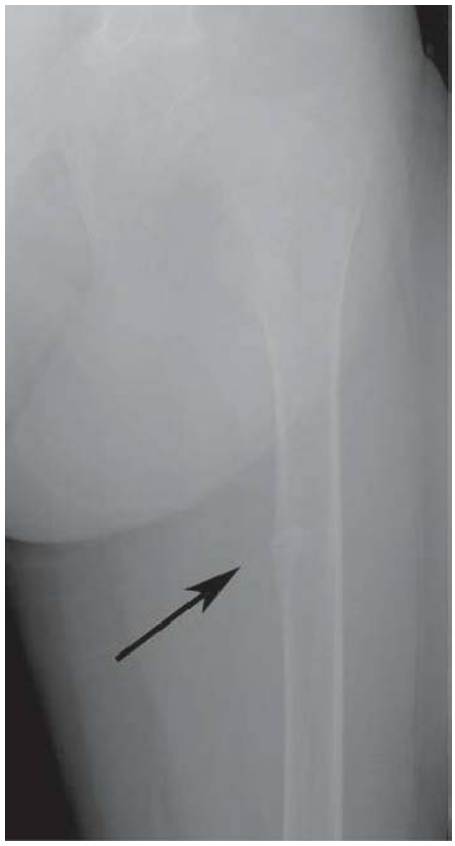


FIGURE 6-7. Renal osteodystrophy. A Looser zone is evident (*arrow*) in the medial femoral diaphysis.

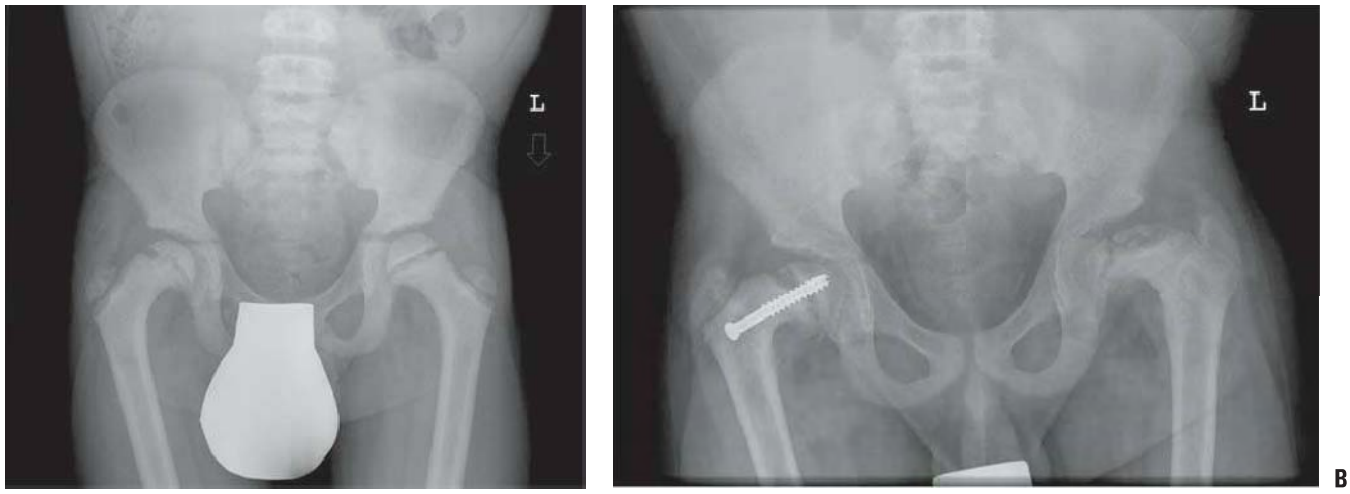
- Vitamin D particularly calcitriol to decrease the secondary hyperparathyroidism as well as to treat clinical rickets or osteomalacia
- Restoration of renal function by transplantation often improves the musculoskeletal manifestations.

Slipped capital femoral epiphysis occurs frequently in patients with renal osteodystrophy and is not common in other presentations of rickets (Fig. 6-8) (130–132). The slip occurs through the metaphyseal side of the physis (126, 133, 134) and occurs at a younger age, in children who are typically small because of their chronic disease. Therefore, stabilization of the slip should permit ongoing growth of the proximal femur if possible. Unstable slips and avascular necrosis are rare in patients with renal osteodystrophy, but avascular necrosis possibly associated with steroid use post transplant has been reported (134). If the child is young and the slip is severe and the bone disease is not yet treated medically, then traction plus medical treatment have shown very good results. When considering the surgical treatment of the slipped epiphysis associated with renal osteodystrophy, the high incidence of bilaterality suggests stabilizing both epiphyses. In young patients, a pinning technique, which allows for growth (smooth pins across the physis), can be considered (133). Hardware cut-out, including pin protrusion into the joint, is more likely with the soft bone of renal osteodystrophy but has generally been associated with inadequate medical control of the hyperparathyroidism (133, 134).

Osteoporosis in Children

Implications to General and Lifelong Health. The National Institutes of Health (NIH) Consensus Panel (2000) has defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increasing risk of fracture." They note that bone strength includes both bone density and bone quality. Childhood osteoporosis can come from numerous primary and secondary etiologies, summarized in Table 6-3.

There are 10 million people in the United States with osteoporosis, and 18 million more with low bone mass at risk for osteoporosis (135). We associate osteoporosis with senescence, and certainly most of the individuals currently



A B

FIGURE 6-8. Renal osteodystrophy in a 12-year-old boy. **A:** An anteroposterior pelvis x-ray reveals an early capital femoral epiphysis on the right. Slipped capital femoral epiphysis is common in renal osteodystrophy and rare in rickets. **B:** Three years after fixation the right proximal femoral epiphysis remains open and stable; the left hip now shows signs of epiphyseal avascular necrosis and fragmentation.

TABLE 6-3 Classification of Childhood Osteoporosis

- **Primary**
  - Structural gene abnormalities
    - Osteogenesis imperfecta
    - Marfan syndrome
    - Ehlers-Danlos syndrome
    - Bruck syndrome
  - Genes important in bone development
  - Homocystinuria
  - Osteoporosis pseudoglioma syndrome
  - Idiopathic juvenile osteoporosis
- **Secondary**
  - Neuromuscular
    - Duchenne muscular dystrophy
    - Cerebral palsy
    - Myelomeningocele
  - Endocrine
    - Growth hormone deficiency
    - Hyperthyroidism
    - Disorders of puberty
  - Drug-related
    - Glucocorticoids
    - Anticonvulsants
- Miscellaneous (methotrexate, heparin, cyclosporine)

affected are old, and not likely seeing paediatric orthopaedists. However, the NIH emphasizes that "sub-optimal bone growth in childhood and adolescence is as important as bone loss to the development of osteoporosis." An epidemiologic study compared rickets mortality in 1942 to 1948 with hip fracture rates in 1986 to 1993 across birth regions in the United States, and found a very high correlation, suggesting that early deficiency of vitamin D could have important effects on the skeleton decades later (136). The recommended intake of calcium for children aged 9 to 17 is 1300 mg per day, and it is estimated that only 10% of girls and 25% of boys meet this minimum requirement (135). While consumption of dairy-based beverages supplying calcium has declined, consumption of carbonated beverages has increased (137). Phosphoric acid is used in cola soft drinks, and teenage girls who drink soft drinks are three to four times more likely to report fractures than those who do not, the association being strongest among active girls drinking cola (138). A meta-analysis of calcium supplementation including 19 randomized trials and 2859 children showed no effect of calcium supplementation alone on BMD at the femoral neck or the lumbar spine (139). Self-reported physical activity in adolescence (but not during adulthood), on the other hand, was a strong determinant of BMD after menopause (140). A meta-analysis of 22 randomized controlled trials of physical activity in childhood showed 1% to 5% increases in bone mineral accrual among the exercising groups, with a greater effect before puberty was complete (141). Vitamin D supplementation has not been so well studied but is receiving increasing attention, with advocates pointing to epidemiologic studies linking vitamin D intake or latitude to lower incidences of cancer and cardiovascular disease as well as to improved bone health (43). A challenge is determining the appropriate level for supplementation of vitamin D, although recent opinion suggests increasing the amount of oral vitamin D_3 to 1000 units per day for both children and adults (43).

Collagen Mutations—Osteogenesis Imperfecta. Osteogenesis imperfecta (OI) or brittle bone disease describes a spectrum of clinical disorders that have in common abnormal bone fragility. The vast majority of patients with OI have disorders of collagen production, which affects either the quantity or quality of collagen produced. Many of these disorders can be traced to specific mutations in collagen genes, but there are myriad such mutations. The phenotype of OI is quite variable and can include mildly affected individuals who are of normal stature without any skeletal deformities, and can extend to include people with extensive bony fragility who suffer dozens of fractures during childhood and are short with deformed bowed extremities and abnormal facial appearance. The most severe form of OI is fatal in the perinatal period.

The orthopaedic surgeon may be involved in operative management of the fractures and deformities that result from OI. Diagnosis of milder forms of OI among children with frequent fractures is easy if the sclerae are abnormal (blue or grey) but can be challenging if they are normal (white). It can be particularly difficult to distinguish mild OI from inflicted injury.

Clinical Presentation. OI is a rare condition with an estimated prevalence of 1 in 15,000 to 1 in 20,000 children (142). The hallmark of OI is brittle bones and the tendency to fracture with recurrent fractures occurring in childhood, in particular during the preschool years. Bone pain is a feature in many patients. It is described as chronic and unremitting and usually relates to old fractures. Muscle weakness may be variously present. Ligamentous laxity and joint hypermobility may be present. Wormian bones are present in the skull in approximately 60% of patients. Abnormal collagen in the eye leads to the blue or gray–blue sclerae classically associated with OI. Abnormal collagen in the teeth leads to dentinogenesis imperfecta (clinically small, deformed teeth which are "opalescent" due to a higher ratio of transparent enamel to opaque dentin), which is present in some, but not all, patients with OI (143–148).

The clinical presentation of OI is heterogeneous across a very wide spectrum. The most utilized clinical classification scheme is based on that first proposed by Sillence in 1979 (148). The Sillence classification has stood the test of time and is a useful way of dividing the phenotype. This classification has recently been modified (146, 149) to incorporate the genetic and biochemical abnormalities (Table 6-4). Greater genetic understanding has led to the addition of extra types to the four OI types initially described by Sillence.

Type I Osteogenesis Imperfecta—Mild. Type I OI is nondeforming. Patients are of normal or low normal height and

TABLE 6-4 Classification of Osteogenesis Imperfecta

Type	Skeletal Manifestation	Sclerae	Teeth	Collagen Defect
I	Mild	Blue	Normal (IA) or dentinogenesis imperfecta (IB)	Quantitative deficiency, but normal collagen
II	Lethal			Abnormal collagen or severe quantitative deficiency
III	Severe	White	Dentinogenesis imperfecta	Abnormal collagen
IV	Moderate	White	Normal (IVA) or dentinogenesis imperfecta (IVB)	Abnormal collagen

do not have limb deformities. They share the hallmark of bony fragility and often have multiple fractures during childhood. Fractures become less common after puberty. Blue sclerae are present in Type I OI. Fifty percent of patients also have presenile deafness (150, 151). This presents typically in the third decade of life and therefore is not helpful for diagnosing children (152). The deafness itself has a conductive component and a sensorineural component and sometimes of a sufficient severity to require surgery for the ossicles of the ears, or cochlear implantation in severe cases (153, 154). Fractures that occur in Type I OI include spiral and transverse fractures of long bones, particularly lower extremity bones. In addition, avulsion type fractures such as olecranon fractures (155) and patellar fractures are common and are related to the decreased tensile strength of the bone because of its underlying low collagen content.

Type II Osteogenesis Imperfecta—Lethal Perinatal. This is the most severe form of OI, and patients die at or shortly after birth. They are born with crumpled femora and crumpled ribs accompanied by pulmonary hypoplasia, which usually leads to death. Central nervous system malformations and hemorrhages are common due to markedly abnormal collagen being produced. Lethal OI can be diagnosed by prenatal utlrasonography. Short broad limbs are identified with low echogenicity and low shadowing, and it is easier to see soft-tissue features such as orbits or arterial pulsations within the fetus. At present, it is not possible to reliably distinguish on prenatal ultrasound between lethal Type II OI and severe but survivable OI Type III described below. Most patients with the lethal form of OI have blue sclerae, though some are born with white sclerae (147, 148, 156, 157).

Type III Osteogenesis Imperfecta—Severe. This is the most severe survivable OI group. These patients have a relatively large skull but undeveloped facial bones leading to a characteristic triangular appearance of the face. The sclerae of patients with Type III OI are described as pale blue at birth, but they become normal in color by puberty. Patients are short with severe limb deformities including bowing and coxa vara (Fig. 6-9). Multiple vertebral compression fractures lead to severe scoliosis and kyphosis and rib cage deformity. Many patients use a wheelchair for mobility or require a walking aid if they walk. Radiographic characteristics include very osteopenic bones with deformity related to previous fracturing. A characteristic popcorn appearance of the epiphysis and metaphysis occurs in early childhood. Up to 25% of these patients will have a coxa vara deformity (158). Pedicles of the vertebrae are elongated. The vertebrae are wedged and may assume a codfish biconcave morphology. Posterior rib fractures are seen. Additional clinical features can include basilar invagination of the skull. This can present with headache, lower cranial nerve palsy, dysphagia, limb hyperreflexia, nystagmus, hearing loss, or quadriparesis. These patients often have multiple fractures when they are born, but they do not have the severe thoracic deformities seen in Type II OI. Fractures heal at the normal rate but recur frequently during childhood particularly in the pre-school years, and some patients have over 100 fractures with this form of OI (156, 157).

Type IV Osteogenesis Imperfecta—Moderate. Type IV OI describes patients with a moderate clinical presentation. Most have short stature and many have bowing and vertebral fractures; although they are not as severely involved as those with Type III OI. Most of them are ambulatory, though some use walking aids. There is a wide range of age at the first fracture and number of fractures in people with Type IV OI. Dentinogenesis imperfecta may be present or absent in these patients. The sclerae are typically white (147, 148).

Additional Types. The four main presentations described by Sillence cover the vast majority of people presenting with OI. There is some overlap in the phenotypes that can be difficult to distinguish—for instance, Type III from Type IV OI. As the genetic defects are understood, there has been the addition of at least three more types of OI, which do not fit into the scheme above. Type V OI is described as hypercallus variety of OI (159). These patients develop profuse amounts of extraosseous callus following their fractures (Fig. 6-10), and the presentation can be confused clinically and radiographically with an osteosarcoma, although Type V OI usually occurs in a much younger child. An additional clinical feature is the ossification of interosseous membranes in between the tibia and fibula, and between the radius and ulna. This leads to the clinical sign of diminished or absent pronation and supination of the forearm, which can help suggest the diagnosis. Over 80% of patients with Type V OI have subluxation or dislocation

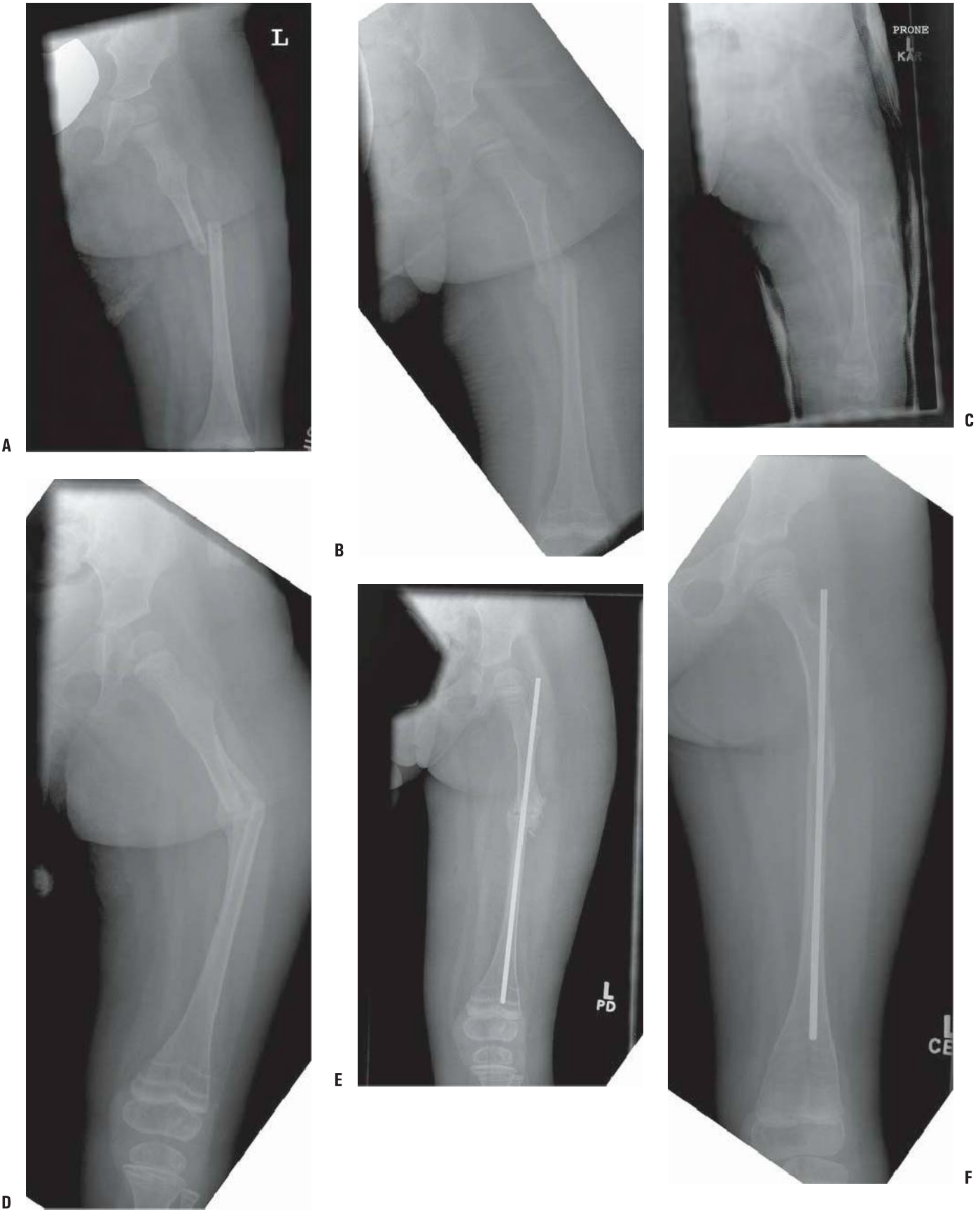


FIGURE 6-9. This female infant with severe OI presented at 19 months of age with a left femoral fracture **(A)** which was treated in a spica cast and healed **(B)**. A refracture was treated in a spica **(C)** with progressive varus. At age 2, a second refracture occurred through the varus malunion **(D)** and was treated with open IM Williams rodding **(E)**. Three years later the femur is intact and has grown distally, as evidenced by the position of the rod and by the transverse metaphyseal lines that occur with each pamidronate treatment cycle **(F)**.

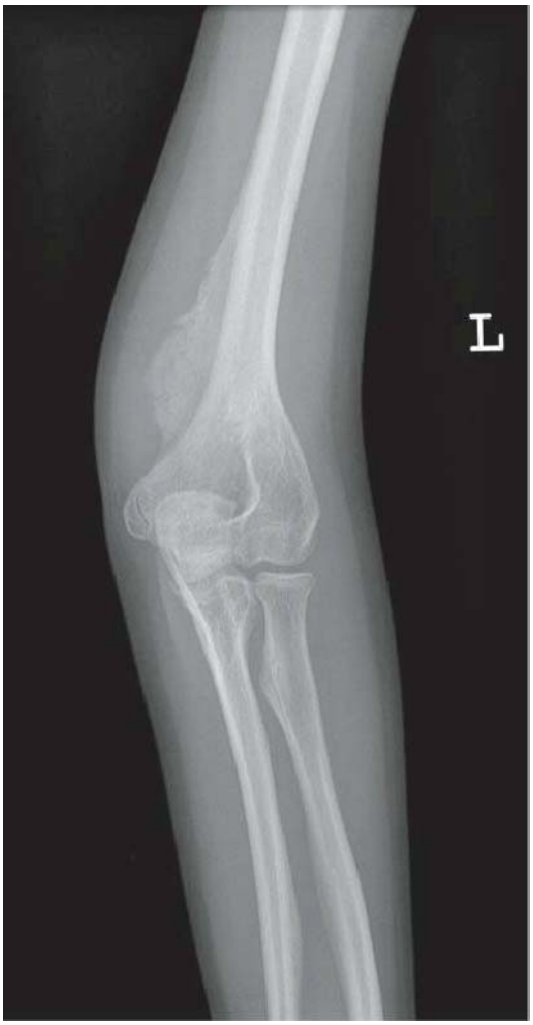


FIGURE 6-10. Osteogenesis imperfecta. The excess callus formation around the distal humerus following injury (no displaced fracture was seen) is typical of type V OI.

of the radial head, which is related to the ossification of the interosseous membrane and may be difficult to treat (160). Type VI OI includes people who phenotypically appear to have moderate or severe OI similar to a Type IV presentation (161). However, they are known to have normal collagen, and they have a defect in new bone mineralization without having any of the biochemical abnormalities or growth plate deformities associated with rickets. The exact etiology of this condition remains uncertain. Type VII OI was initially described in a cohort of First Nations individuals from Quebec, Canada (162). These patients are rhizomelic with deformities characteristically coxa vara of the long bones. The bone is histologically similar to that as seen in Type I OI. Linkage analysis shows that the defect is on chromosome 3 and, therefore, is not in a collagen gene.

Etiology of Osteogenesis Imperfecta. Most presentations of OI are caused by mutations within the collagen 1A1 gene found on chromosome 7q, or mutations in the collagen 1A2 gene found on chromosome 17q. The complete list of mutations found is kept up-to-date at the Osteogenesis Imperfecta Mutation Database at www.le.ac.uk/genetics/collagen.

Two different types of mutations produce OI. OI Type I, which is the mild form, is a *quantitative* defect in collagen production resulting from a silenced allele of the collagen 1A1 gene (146, 163, 164). This is usually the result of a premature stop code on within the gene. This results in the production of nonsense messenger RNA instead of proper messenger RNA coding for the preprocollagen molecule. The nonsense messenger RNA is detected and destroyed, and the result is production of a diminished number of alpha 1 chains, and consequently a decreased quantity of normal collagen being produced. With the decreased quantity of collagen, the bone is weakened and more susceptible to microfractures. Bone can sense its mechanical environment, and microfractures cause a new round of bone removal and reformation. This leads to constant activation of bone remodeling in OI. This demands an increased transcriptional activity of Type I collagen and induces an increased number of osteoclasts and an increase in the excretion of collagen degradation of products. Bone turns over rapidly but remains of poor quality. When growth ceases at puberty, and the transcriptional activity demand is reduced and bone turnover can slow down, then the bone strength and architecture becomes closer to normal and the fracture rate drops.

OI Types II, III, and IV are usually caused by production of *abnormal types of collagen* (146, 165). The collagen molecule is a triple helix formed by spontaneous self-assembly of three long linear procollagen molecules. These procollagen molecules have a typical repeating amino acid pattern of glycine XY-glycine XY-glycine XY. Glycine appears every third position because it is the smallest amino acid and can be folded into the interior of the triple helix. Glycine substitutions place a larger amino acid where the glycine residue belongs, so the collagen triple helix cannot assemble appropriately. The collagen molecule begins assembling at the C-terminal end and assembles toward the N-terminal end. If the mutation substitutes for a glycine close to the C-terminus at the beginning of the molecule, then a very short strand of abnormal gene product is produced and the corresponding clinical diseases are severe. If the glycine substitution mutation is toward the distal N-terminus end, then a longer partial collagen molecule can be formed, and the clinical phenotype is less severe.

The primary defect in OI is the osteoporosis produced by abnormal quantity or quality of collagen. Mechanically the bone is more ductile, rather than being more brittle (166). To this is added secondary osteoporosis caused by immobilization following fractures or surgery, or because of decreased physical activity and weight bearing with severe deformity. Prevention of the secondary osteoporosis is an important concept when treating fractures, planning surgery, or recommending general care.

Diagnosis. The clinical diagnosis of OI is the mainstay. There is no single laboratory test that distinguishes people with OI from those with normal bone. The clinical features of severe OI Type II and Type III are distinct enough that

physical findings and plain radiography are usually sufficient to arrive at a diagnosis. Patients with Type I OI have blue or blue–grey sclerae and are readily identified clinically. Normal babies may have blue sclerae until 1 year of age, so this finding is only diagnostic in the older child. Patients with mild presentations of Type IV OI are easy to diagnose if they have dentinogenesis imperfecta, but those with normal teeth may benefit from additional investigation depending on the purpose of making the diagnosis. Dual energy x-ray absorptiometry (DEXA) scanning shows low lumbar and femoral BMD in mild OI patients (167, 168). Published values for BMD in healthy normal children are available for comparison (169). Caution must be exercised in interpreting DEXA scans in children, and overdiagnosis of osteoporosis is reported to be frequent (170). This is because DEXA scanning reports BMD per square centimeter surface area of bone, ignoring the third dimension (thickness of the bone in the path of the photon) which is larger in adults leading to greater area density even if true volumetric density were the same.

Dozens of individual mutations have been found within collagen 1A1 and collagen 1A2 genes producing the main phenotypes of Type I, Type II, Type III, and Type IV OI (146, 156, 157, 164, 171). As such, many new patients often have new mutations specific to themselves. Accordingly, a DNA-based genetic test for OI is usually performed only at reference laboratories at present. An intermediate level of testing involves culturing dermal fibroblasts and studying the amount and quality of collagen that they produce. Quantitatively, abnormal collagen production can be detected in 87% of individuals with known OI. Conversely, 13% of individuals with known OI would be missed by a cultured dermal fibroblast test. One common question is whether a person has OI or inflicted trauma. OI is very rare and inflicted injury remains significantly more prevalent. Clinical diagnosis remains a gold standard to distinguish these two entities and cultured dermal fibroblast testing is not considered useful as a routine part of such investigation (172). In cases with legal implications, positive findings in the history, past history, family history, clinical examination, or properly interpreted DEXA scan may assist in the diagnosis of osteoporosis or OI. OI cannot be entirely ruled out in patients with negative findings, but is a highly unlikely diagnosis in the presence of positive findings suggesting child abuse (discussed elsewhere). Finally, a diagnosis of OI does not exclude the possibility of child abuse.

Osteogenesis Imperfecta—Medical Treatment. Cyclical administration of intravenous bisphosphonates has recently become popular in the pharmacologic management of *severe* OI, but cannot currently be recommended for mild OI. Bisphosphonates are widely used drugs based on the pyrophosphate molecule, which is the only natural inhibitor to bone resorption. The drugs all bind strongly to bone, with the primary action at the level of the osteoclast. Osteoclast toxicity from ATP analogues is thought to be important to the mechanism of action.

Clinical reports of the use of bisphosphonate in OI began with case series, and much of the published evidence remains case series. Glorieux reported the effects of bisphosphonate treatment in uncontrolled observational study of 30 patients with severe OI (173). The intravenous dosing given was 3 mg/kg of pamidronate per cycle by slow intravenous infusion at 4-month intervals. All patients were given 800 to 1000 mg calcium per day and 400 international units of vitamin D per day. Marked improvement in patient's clinical status was noted. There was an average of 42% per year increase of BMD. There was an increase in the cortical width of the metacarpals and in the size of the vertebral bodies. Average number of fractures dropped from 2.3 per year to 0.6 per year. No nonunions or delayed unions of any fractures were noted. Patients reported a marked reduction of bone pain 1 to 6 weeks following initiation of treatment. The only adverse effect noted was the acute phase reaction comprising fever, back pain, and limb pain on day 2 of the first cycle. This was treated with acetaminophen and did not recur with subsequent infusion cycles. Patient's mobility improved in 16 of the 30 patients treated with no change in 14. Growth rates increased. Patients under 3 years of age showed a faster and more pronounced effect of the bisphosphonate. The direct effect of the bisphosphonate is decreasing bone resorption and turnover. The resulting decreasing bone pain and fractures resulted in increased weight bearing and mobility. It is likely that the increased weight bearing and mobility resulted in further strengthening of bone and muscle.

Bisphosphonate treatment has become a standard for severe OI, and the clinical literature supporting it now includes randomized clinical trials. A Cochrane review found eight randomized clinical trials supporting the use of bisphosphonates in severe OI (174). All trials showed an increase in BMD, and adequately powered trials showed a decrease in fracture rates. Oral or IV bisphosphonates were both effective. A high-quality placebo-controlled trial showed oral olpadronate effective at increasing BMD and decreasing fractures (175). Improvements in functional outcomes and quality of life have not been shown in randomized trials to date, although case series suggest they are present (176, 177). It should be noted that this drug does not address the basic abnormality underlying OI, but it does alter the natural course of the disease. Radiographs of patients with OI treated with cyclic intravenous bisphosphonates show characteristic dense sclerotic lines which form at the growth plate, one per treatment cycle (178).

Duration and continuity of bisphosphonate therapy has not been optimized in children. Stopping bisphosphonate treatment while rapid growth remains may result in a marked reduction in metaphyseal bone mineral content (179), and prolonged use has not been shown to adversely affect the mechanical properties of bone in children with OI (180), so there is a tendency to continue treatment, perhaps at a lower dose, while growth remains. Fracture healing in children is not impaired by bisphosphonates, and the evidence regarding osteotomy treatment is contradictory (181, 182) with one series reporting no delay and another reporting delay—in the latter case, the osteotomies were done open and with powered saws. Lower extremity nonunions in the presence of rods are often asymptomatic and clinically unimportant, but distal humeral

malunions can be disabling and challenging to treat (183). Some surgeons recommend discontinuing bisphosphonate treatment for 6 weeks before and after planned osteotomy surgery, but this recommendation may change as evidence accumulates.

Concerns about the potential negative consequences of using bisphosphonates over the long term still exist. Pamidronate binds strongly to bone and is released only slowly, so demonstrable amounts have been reported in the urine of patients many years after the cessation of therapy (184). Animal studies show bisphosphonate crosses from the placenta to the fetus, although no adverse fetal outcomes have yet been reported in series of mothers who were taking bisphosphonates prior to or during pregnancy (185, 186). Similarly, despite the concern about osteonecrosis of the jaw in adult patients taking bisphosphonates, there is no clinical evidence of this complication among 64 pediatric patients with 38 dental procedures (187) nor is the author aware of case reports of this complication in children.

Caution must be exercised in extending the indications for bisphosphonate treatment to patients with milder forms of OI. Reported clinical results apply only to patients with severe OI. Osteopetrosis is a reported complication of bisphosphonates in humans (188). Animal studies suggest reduced longitudinal bone growth with these drugs (189–191). Randomized controlled clinical trials are needed before routine clinical use of bisphosphonates in milder forms of OI is considered.

Other medical treatments for OI include anabolic agents, specifically human growth hormone. Human growth hormone is an anabolic agent, therefore, stimulates increased bone turnover—causing a higher demand for collagen transcription and perhaps exacerbating the underlying abnormality while attempting to ameliorate the decreased stature. Because growth hormone may have both beneficial and negative effects in OI, clinical research results are required before indications can be stated. We suggest at present that growth hormone be used in OI patients only in the context of clinical research studies.

Osteogenesis Imperfecta—Surgical Treatment. Patients with mild (nondeforming) OI require little modification of standard surgical treatments, whereas those with severe (deforming) OI require multiple specialized surgical techniques and implants.

A newer elongating rod design, the Fassier-Duval rod (Figs. 6-11 to 6-18) has cancellous screw threads at either end to provide stable anchorage in the epiphysis or metaphysis (192). The need for revision due to bone growth and rod migration was reported as higher for nonelongating rods in one series (193), but approximately equal to that seen with elongating rods in another (194). Methods of rod exchange via percutaneous techniques have been described (195, 196), and a stereotactic device to assist this has been developed (196) but is not in wide clinical use.

Tiley reported on 129 roddings among 13 children, of whom 11 maintained or gained the ability to ambulate (197). Most reports suggest that ambulation is improved by rodding (198–201), but one emphasizes the possibility of ambulatory status worsening in a large number of patients (202). The ultimate walking prognosis in OI is much more strongly influenced by subtype than by treatment (203–205), but modern combinations of medical and surgical treatment combined with rapid advances in the understanding of the biology of the disease may one day change this. Current trends are toward percutaneous or minimal open osteotomies, multiple bones rodded simultaneously, elongating rods, and postoperative splinting instead of casting with early supervised ambulation (206).

The Spine in Osteogenesis Imperfecta. Scoliosis (Fig. 6-19) can be very challenging to treat in patients with OI (207–216). Progressive curves beyond 25 degrees are more common in Type III OI, and are associated with lower BMD (217). There is no evidence yet that bisphosphonate treatment prevents scoliosis. Bracing appears to be ineffective at preventing curve progression even when curves are small (213, 216). Patients with large progressive curves may suffer from pulmonary compromise, and bracing can cause rib deformities which worsen this. It is unknown whether operative management of the scoliosis leads to improved pulmonary function, quality of life, and survival. Accordingly, operative decision making must be individualized for each patient. Spinal fusions have a higher complication rate in OI, with 20 patients of 60 experiencing a total of 33 major complications (213). The most common complications were blood loss >2.5L (9 cases), intraoperative hook pullout (5 cases), postoperative hook pullout (5 cases), and pseudarthrosis (5 cases). Strategies to prevent hook pullout include load sharing via segmental instrumentation, supplementation of hook site bone with methylmethacrylate, and consideration of fusion without instrumentation. Preoperative medical treatment (bisphosphonate) to strengthen the bone is logical but results are not yet reported. Progression of the curve postoperatively, with or without pseudarthrosis, may occur (213). The natural history, expectations, likelihood of complications, and likelihood of success must be carefully assessed for each patient, and decisions not to embark on surgical reconstruction are sometimes correct.

Spondylolysis of the lumbar spine was found in only 5.3% of patients with OI at a national referral program clinic, a rate similar to that in the normal population (218).

Cervical Spinal Conditions in Osteogenesis Imperfecta. Anterior decompression and posterior stabilization of the cervical spine for basilar invagination was reported in 20 patients with a median follow-up of 10 years. Twenty-five percent of patients had recurrence of deformity or death, 15% had no improvement, and 60% improved or stabilized (219). In addition to surgery for basilar invagination, some OI patients have required anterior corpectomy for upper cervical kyphosis with spinal cord compression (220) and some have required shunting for obstructive hydrocephalus, or craniotomy for subdural and epidural bleeding following no or minor trauma (221).

Text continued on page 161

Fassier-Duval Technique for Growing Rods of Femur in Osteogenesis Imperfecta (Figs. 6-11 to 6-18)

FIGURE 6-11. Fassier-Duval Technique for Growing Rods of Femur in Osteogenesis Imperfecta: Step 1. Perform the first osteotomy through a lateral incision where the proximal apex of deformity will permit a straight rod to reach the trochanter. Image intensifier control is recommended. Pay extra attention to the lateral view when planning this osteotomy as there is often marked apex anterior angulation in addition to a varus deformity.

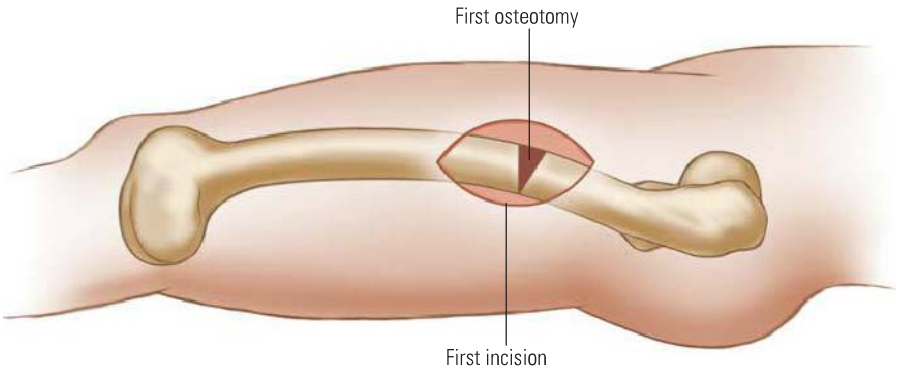


FIGURE 6-12. Step 2. Ream the proximal fragment up to the tip of the greater trochanter over a flexible guide wire.

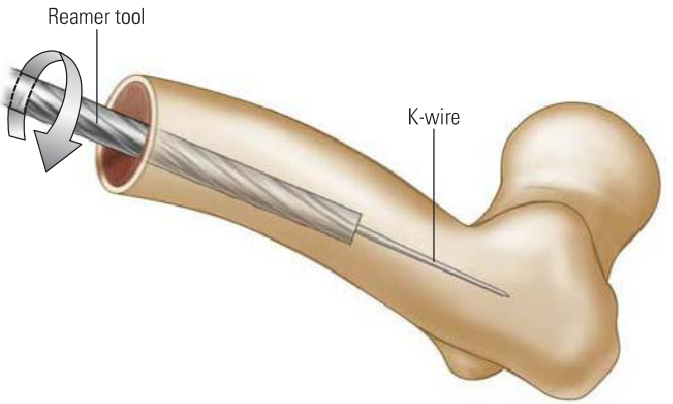
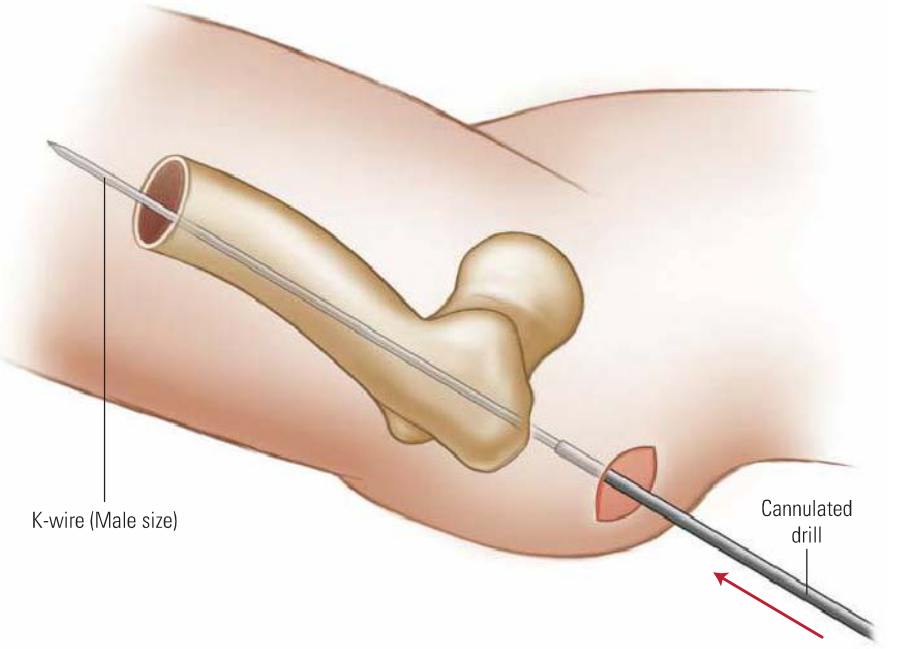


FIGURE 6-13. Step 3. Perform a second more distal osteotomy if needed to place a straight rod. Insert a male size K-wire retrograde from the more distal osteotomy and make an incision in the buttock to allow the K-wire to exit proximally.



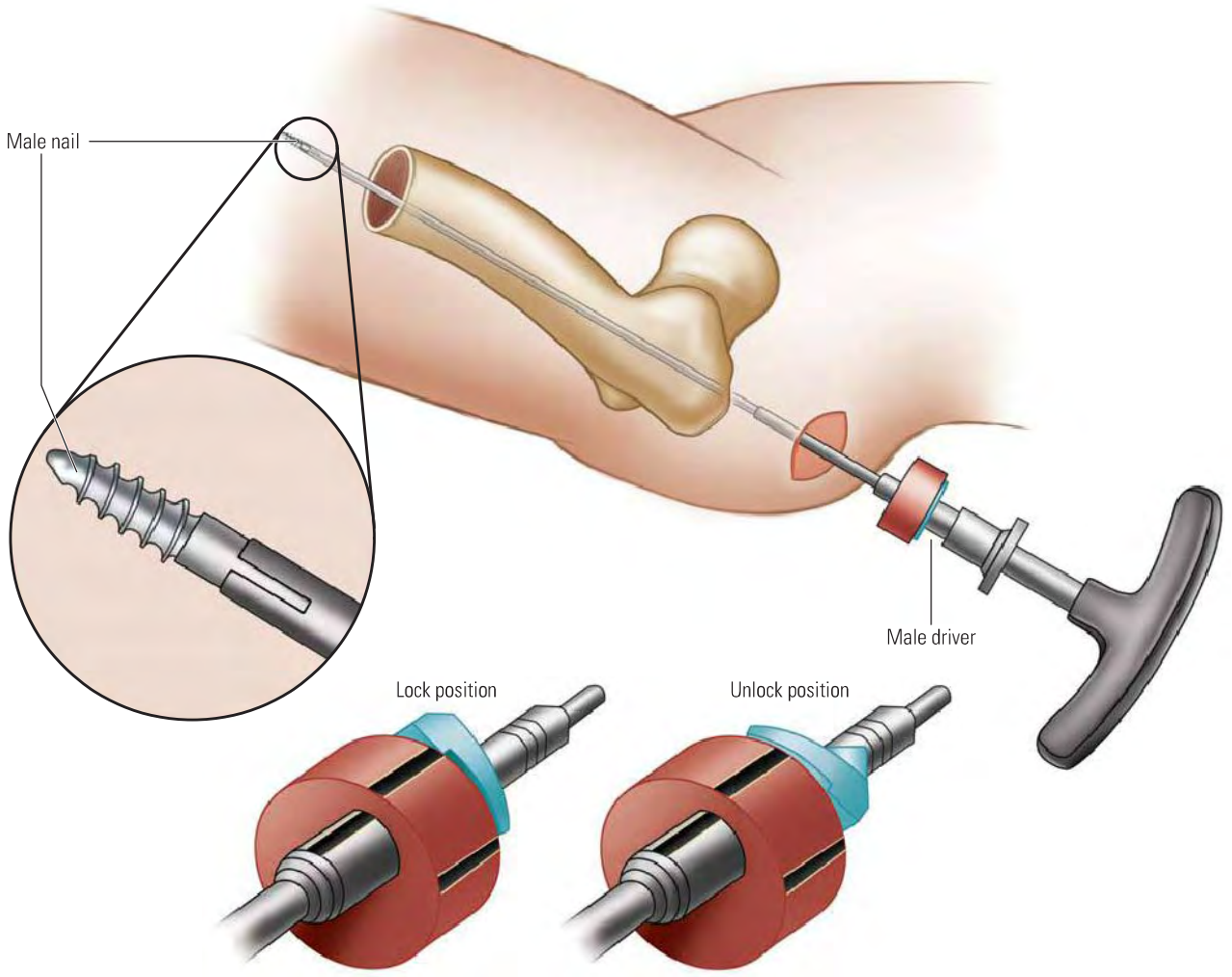


FIGURE 6-14. **Step 4.** Introduce the male driver over the K-wire. Remove the K-wire and introduce the male nail into the driver working retrograde through the more distal osteotomy.

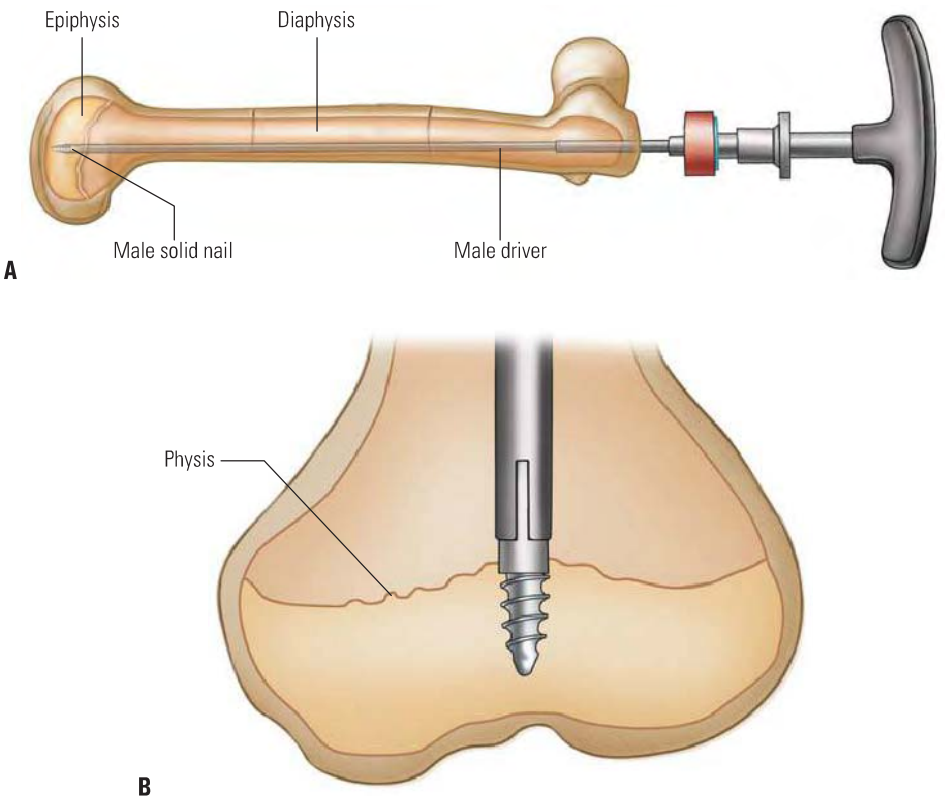


FIGURE 6-15. **Step 5. A:** Reduce the femur and push the male nail and driver into the distal fragment. Avoid bending the nail. **B:** Screw the threaded portion into the centre of the epiphysis.

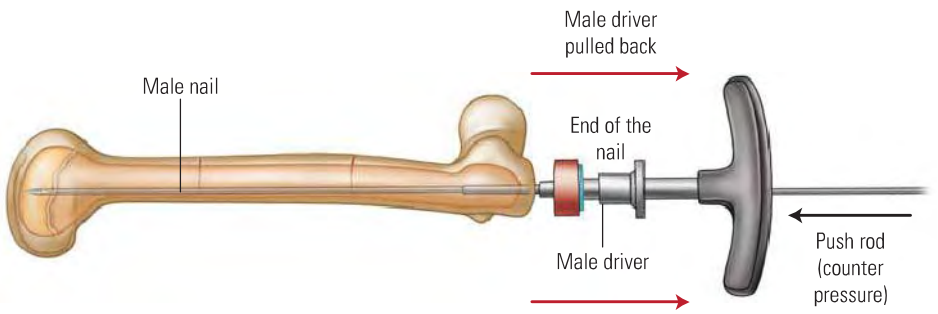


FIGURE 6-16. **Step 6.** Stabilize the male nail with a pushrod while removing the male driver.

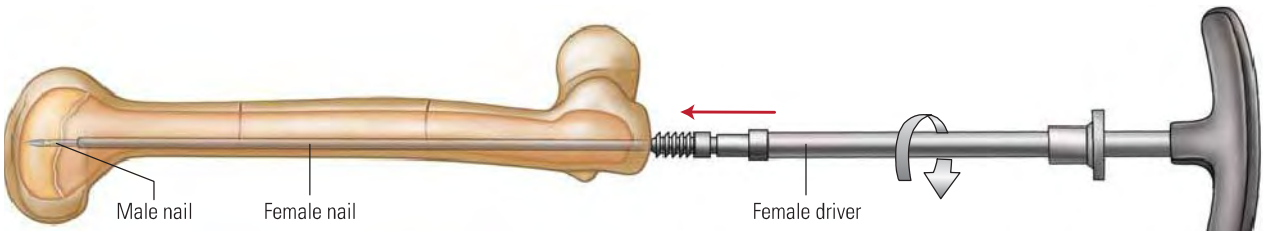


FIGURE 6-17. **Step 7.** Introduce the precut hollow female nail over the male nail and screw it in to the trochanter.

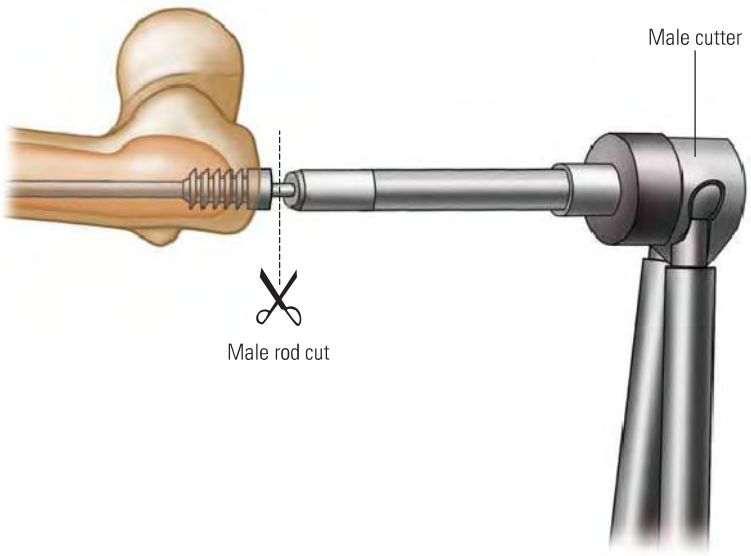


FIGURE 6-18. **Step 8.** Cut the male nail leaving 10 to 15 mm prominent and confirm a smooth end for gliding with growth.

Juvenile Idiopathic Osteoporosis. Idiopathic juvenile osteoporosis is a rare condition (222). Onset is typically 2 to 3 years prior to puberty, and patients present with vertebral (Fig. 6-20) or long bone fractures and bone pain. Fractures are typically metaphyseal in location. Kyphosis, scoliosis, and pectus carinatum deformities can be present. BMD is decreased 2.5 standard deviations below age-appropriate norms. Idiopathic juvenile osteoporosis is a diagnosis of exclusion, other primary and secondary causes of osteoporosis must be excluded (Table 6-3). There are no lab abnormalities specific to the diagnosis and the genetic cause is as yet unknown. Treatment includes optimizing calcium and vitamin D intake and promoting physical activity including weight bearing and strength training but avoiding trauma. Bracing can be used to treat vertebral pain and to prevent progression of kyphotic deformities (223). Judicious use of bisphosphonate therapy may be considered in severe cases. A remarkable remission of the condition at puberty is common.

Other Forms of Primary Osteoporosis in Children. As well as OI and idiopathic juvenile osteoporosis, there are several other primary causes of reduced BMD in children. Children with Ehlers-Danlos syndrome, Marfan syndrome, and homocystinuria have reduced bone mass. Those who suffer fractures or bone pain as well can be considered to have a form of primary osteoporosis, but fractures are not as typical a feature of these conditions as they are of OI. Like OI, these conditions are based on known deficiencies in the production of structural proteins. They are discussed in other chapters.

Bruck syndrome is a rare primary form of osteoporosis. The phenotype is similar to OI with thin bones, fractures, bone pain, and blue or white sclerae. Joint contractures are a distinctive clinical characteristic of Bruck syndrome (224). The condition is a result of failure to crosslink collagen fibrils, which is specific to bone tissue (225).

Osteoporosis pseudoglioma syndrome is an autosomal recessive disorder phenotypically similar to OI but accompanied

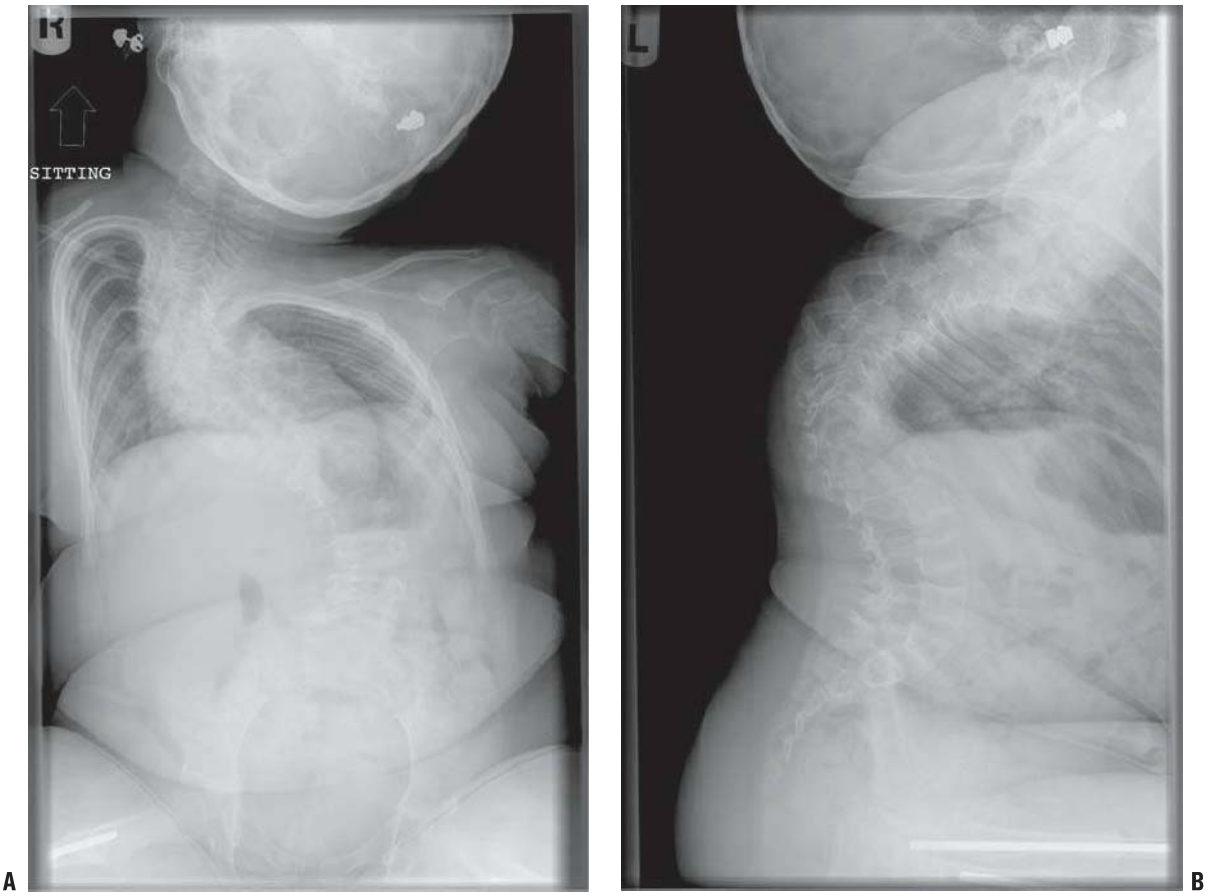
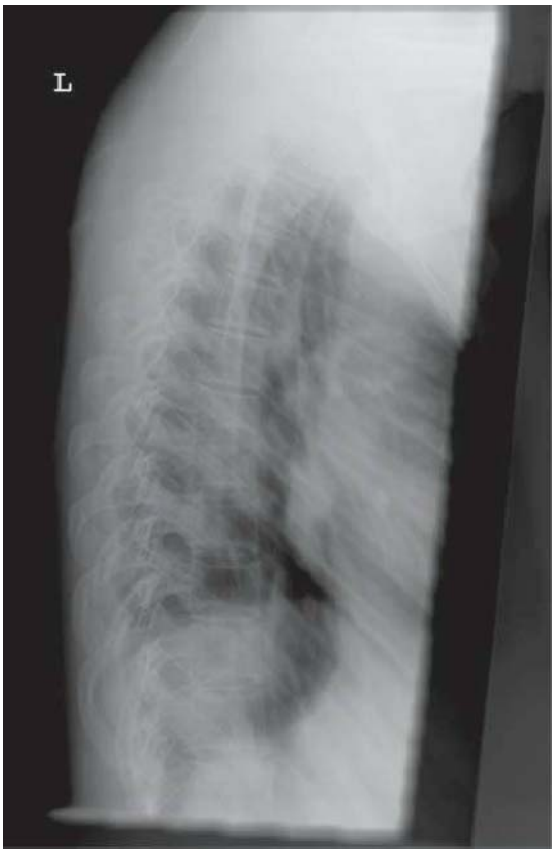


FIGURE 6-19. **A,B:** Osteogenesis imperfecta. Marked spinal deformity in a 5-year-old girl with severe OI.

FIGURE 6-20. Juvenile idiopathic osteoporosis. This 14-year-old boy has marked osteoporosis evident on plain radiographs (DEXA scans indicated bone mineral densities 2.8 standard deviations below mean) and a healed compression fracture at T7.



by congenital blindness due to hyperplasia of the vitreous (226, 227). The mutation is in the low-density lipoprotein receptor related protein 5 gene (228). Treatment with bisphosphonates has been successful (229). Operative management of fractures with IM rodding techniques has encountered complications related to severe fragility of bone (230).

Secondary Osteoporosis in Children. Bone mass responds to biochemical, hormonal, and mechanical signals as described in the first part of the chapter. Interference with normal homeostatic mechanisms leads to a reduced bone mass—for example, many children have disuse osteopenia following fracture treatment. Resumption of load bearing after healing allows this to normalize. In conditions where weight bearing is reduced, persistent low bone mass can lead to low energy fractures and a fracture cascade of repeated fractures in the same extremity.

Neuromuscular Disorders. The central nervous system exerts direct control over BMD. The fat-derived hormone leptin acts on hypothalamic neurons, which mediate bone mass via the sympathetic nerves (231–234). Clinical significance of this recent finding has not been elucidated, but it may become important in managing osteoporosis and related regional conditions such as reflex sympathetic dystrophy. At present, the management of neuromuscular osteoporosis focuses on the downstream effects of the neuromuscular abnormalities on load bearing and nutrition.

Low bone mass is observed in cerebral palsy (CP) patients (235–239). Typically, it is nonambulatory patients with the lowest bone masses who are at risk for pathologic and low energy fractures, but the reduced bone mass has been observed in the affected limb of ambulatory hemiplegics (240, 241), suggesting that both weight bearing and muscle forces play a role in establishment and maintenance of bone mass. Undernutrition is the second most important predictor of low bone mass in CP patients, after ambulation (239, 242). Fractures and a "fracture cascade" of increasing disuse osteoporosis from treatment-related immobilization can cause significant problems for many patients (243, 244). Fracture prevalence among children and adolescents with moderate to severe CP was 26% in one study (239). The orthopaedic surgeon should focus as much on the prevention as on the treatment of osteoporosis in the CP population. Increasing weight bearing, optimizing nutrition, and minimizing the extent and duration of immobilization following surgery are important. A controlled trial of weight bearing in CP patients showed significant increases in femoral neck bone mineral content (245). Medical treatments including vitamin D and calcium (246) or bisphosphonates (236, 247, 248) have also been reported to increase BMD in CP patients, although the precise indications for their prescription are unclear. More recent evidence shows that BMD returns toward pretreatment baseline in nonambulatory CP patients after discontinuation of bisphosphonate therapy (249). Approximately one-third of children without CP sustain a fracture during childhood, so the 26% fracture prevalence among children with CP does not seem out of line. Accordingly, if weight bearing is easy to achieve and enjoyable for the child, it can be recommended; but if extensive surgery, elaborate standers, and many hours of professional care are required, then perhaps it is not of benefit to the child.

Patients with Duchenne muscular dystrophy (DMD) lose bone mass as lower extremities weaken, with bone densities 1.6 standard deviations below the mean while still walking and 4 standard deviations below the mean once nonambulatory. Of 41 boys followed, 18 sustained a fracture, 12 of which were lower extremity fractures, and 4 of which caused loss of ambulation (250). BMD has been reported as lower among boys treated with steroids (prednisone) than among untreated boys with DMD (251). Deflazacort is a steroid medication which preserves muscle strength, ambulation, and respiratory function as well as prevents the onset of scoliosis. Despite being a glucocorticoid analogue, it is reported as having bone sparing effects (252) and randomized trial evidence (in juvenile arthritis) shows less bone loss among deflazacort treated patients compared with prednisone treated patients (253). Vertebral fractures have been reported in patients treated with deflazacort (254) while they are rare among untreated boys (250). A single clinical case series reported positive effects on BMD following daily oral alendronate for 2 years, with better response seen in younger boys (255).

Endocrine/Metabolic Disorders

Growth Hormone Deficiency. Growth hormone deficiency results in extreme short stature and low muscle mass. BMD is low in both adults and children, and adults have a 2.7 times increased fracture rate compared with normal controls (256). Treating the deficiency with growth hormone improves longitudinal growth and muscle mass as well as improving calcium absorption, so exerts beneficial effects on the osteoporosis both mechanically and biologically. Improved BMD with growth hormone treatment has been documented in adults but requires further study in children (257, 258).

It is noteworthy that growth hormone deficiency is the second most common endocrinologic cause of slipped capital femoral epiphysis (after hypothyroidism). Ninety-two percent of children with growth hormone deficiency and SCFE present with the slip *after* growth hormone treatment has been initiated perhaps because the growth plate becomes more active, and potentially mechanically weaker relative to the larger size of the body. The prevalence of bilaterality in slips with endocrinopathies has been reported to be as high as 61%, so prophylactic pinning of the contralateral side is suggested by some (259). Among 2922 children followed prospectively while receiving growth hormone in Australia and New Zealand, only 10 slipped epiphyses were reported by clinicians performing active surveillance for complications (260).

Hyperthyroidism. Hyperthyroidism leads to bone loss through increased bone turnover. T3 directly stimulates osteoblasts, which results in linked osteoclast activation and bone resorption. The increase in serum calcium and phosphate suppresses PTH and 1,25-dihydroxyvitamin D production, which decreases calcium and phosphate absorption and increases calcium excretion. The net result is bone resorption in a high

turnover state (222). Treatment of the underlying disease to achieve a euthyroid state is the appropriate management for the osteoporosis.

Disorders of Puberty. One-third to one-half of adult bone mass is accrued during the pubertal years, and sex steroids are necessary for this accelerated bone mineral accrual. Mineral accrual lags behind the longitudinal growth spurt by a year or two, perhaps partially explaining the increased fracture rate documented during and just after the growth spurt (261). Over the past 30 years, there has been a statistically significant increase in the incidence of distal forearm fractures in adolescents, but it is unclear whether this relates to changes in diet or in physical activity (262).

Precocious puberty results in accelerated growth and bone mineral accrual. It can be treated with GnRH analogues to preserve epiphyseal function and allow attainment of greater final height. Such treatment does not adversely affect peak bone mass. Constitutionally, delayed puberty in boys is associated with lower BMD, but it is unclear whether testosterone treatment improves overall mineral acquisition (222).

Athletic amenorrhea is common among young women training for endurance sports, particularly distance running. Thirty-one percent of college-level athletes not using oral contraceptives reported athletic amenorrhea or oligomenorrhea (263). Athletic amenorrhea plus disordered eating plus osteoporosis has been dubbed the "female athlete triad" (264, 265). The full triad is rare among athletes (266) and was found to be nonexistent among female army recruits (267). Not all sports are equal in propensity to bone loss. Gymnasts exhibit higher bone mass than do runners despite similar prevalence of amenorrhea, (268), gymnasts have both higher muscle strength (269) and higher serum insulin like growth factor 1 (IGF-I) (270) than do runners and these are both protective of bone mass. It must be remembered that for the general population, more exercise means more bone, as has been demonstrated in randomized trials of physical activity in prepubescent and pubescent children (271, 272).

Untreated anorexia nervosa is associated with 4% to 10% trabecular and cortical bone loss per year (273). The long-term prevalence of fractures among people with anorexia nervosa is 57% at 40-year follow-up, 2.9 times higher than that in the general population (274). Estrogen alone is insufficient to restore BMD, particularly if nutrition is compromised (275, 276). Restoration of body mass, provision of adequate calcium and vitamin D, and correction of the hormonal environment should all occur.

Primary amenorrhea from pure dysfunction of the hypothalamic–pituitary axis was associated with osteoporosis in three and osteopenia in 10 of 19 girls (ages 16 to 18), compared with 0 of 20 controls with regular cycles (277).

Drug Related

Glucocorticoids. Steroids are commonly used to treat a variety of acute and chronic medical conditions. Frequent short courses of oral glucocorticoids (for asthma exacerbations) have been shown not to adversely affect BMD in children (278), but chronic glucocorticoid use is a well-established cause of osteoporosis and is common among patients with juvenile arthritis, leukemia, and organ transplantation. The underlying mechanism includes osteoblast apoptosis and decreased intestinal calcium absorption and renal reabsorption (222). Deflazacort is a bone sparing glucocorticoid (252) and randomized trial evidence (in juvenile arthritis) shows less bone loss among deflazacort treated patients compared with prednisone treated patients (253). In adults using glucocorticoids, there are now multiple trials demonstrating that bisphosphonates and teriparatide (a synthetic analogue of PTH) are useful for prevention and treatment of bone loss, and for prevention of fractures (279–284). Case series of bisphosphonate use in children on chronic glucocorticoid treatment have shown similar promising results; however, teriparatide is not used in children because of the potential for malignancy in growing bone (255, 285, 286).

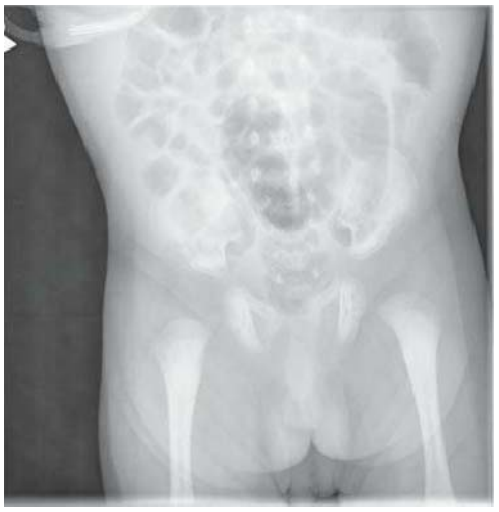
Anticonvulsants. An association between altered bone mineral metabolism and anticonvulsant drugs has long been discussed (287–293), although the exact mechanism by which anticonvulsants interfere with bone metabolism remains unknown. Induction of liver enzymes with increased vitamin D catabolism has been proposed (294, 295), but vitamin D metabolism has been conflictingly reported as normal (296, 297). There is laboratory evidence that phenytoin and carbamazepine exert a direct effect on bone cells (298). Quantitative CT studies of the distal radius in patients using carbamazepine or valproic acid (for isolated epilepsy, without CP) showed decreased trabecular BMD but a compensatory increase in cortical BMD in a high bone turnover state (299). A controlled trial has shown that treatment with vitamin D and calcium increases BMD in children with severe CP, who are receiving anticonvulsants (246).

Miscellaneous. Other drugs reported to cause osteopenia and osteoporosis in children include methotrexate, cyclosporine, and heparin. Little information on prevention and treatment of the iatrogenic osteoporosis in children is available (222).

SCLEROSING BONE CONDITIONS IN CHILDREN

Osteopetrosis. Osteopetrosis is the most common and the most well-known of the sclerosing bony dysplasias. All of these conditions are characterized by an imbalance between the formation and the resorption of bone favoring formation. In osteopetrosis, it is decreased or completely failed resorption of bone due to an osteoclast defect which tips the balance to favor formation.

Three clinical presentations of osteopetrosis are traditionally described (300). The infantile or autosomal recessive form is the most severe and can be fatal in the first decade. Patients present with pathologic fractures or with an exceedingly dense radiographic appearance of the bones (Fig. 6-21). They can have cranial nerve problems including optic nerve compression and blindness, facial nerve dysfunction, and sensorineural deafness due to narrowing of the skull foramina. They can have bone pain related to fractures or stress fractures.



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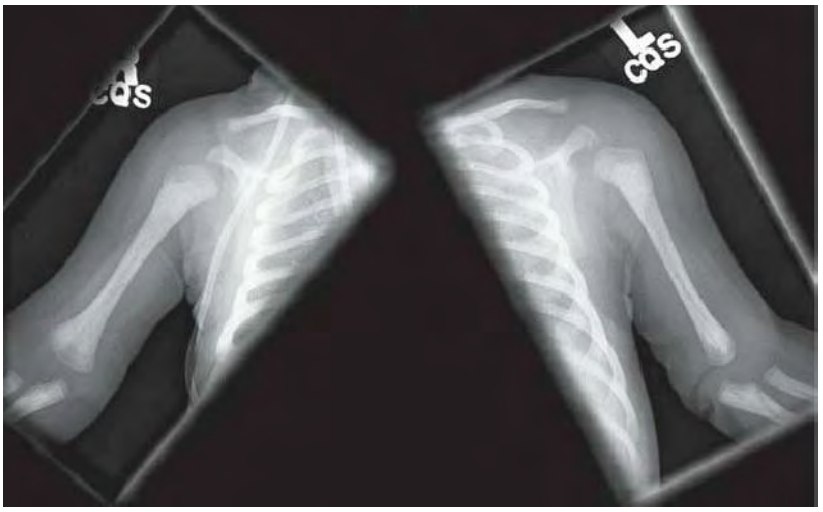

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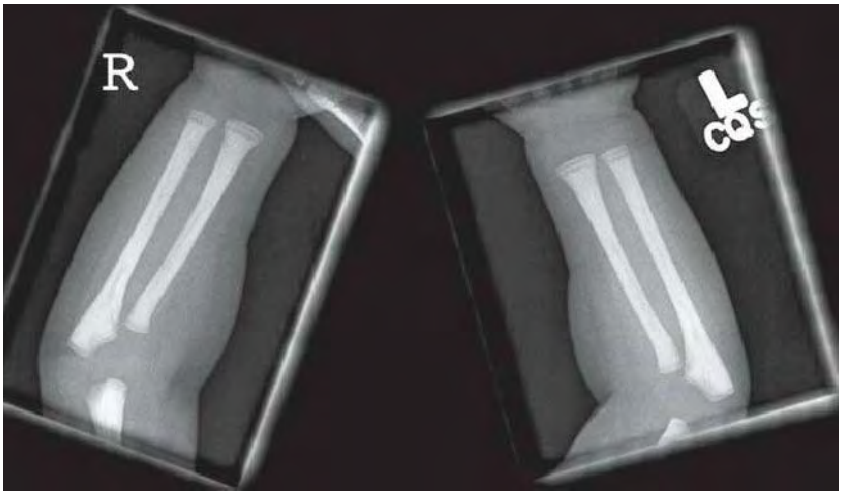

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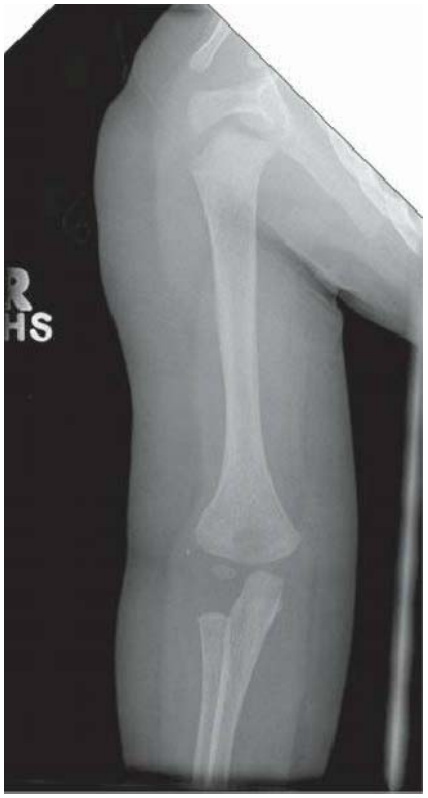

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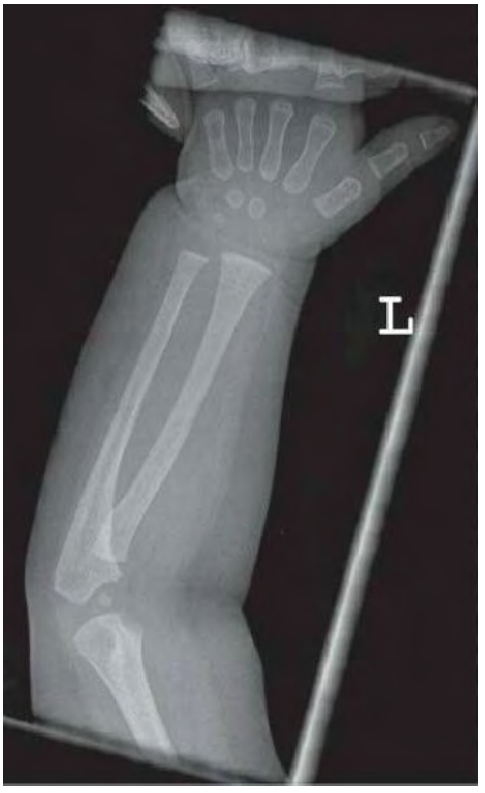


E

FIGURE 6-21. Six-month-old male infant with severe osteopetrosis and pancytopenia. **A–E:** Dense sclerotic bones at the pelvis **(A)**, humerus **(B)**, and forearm **(C)**, without evident medullary cavities. **D, E:** After successful bone marrow transplant the bony architecture in the humerus **(D)** and forearm **(E)** were normalized.

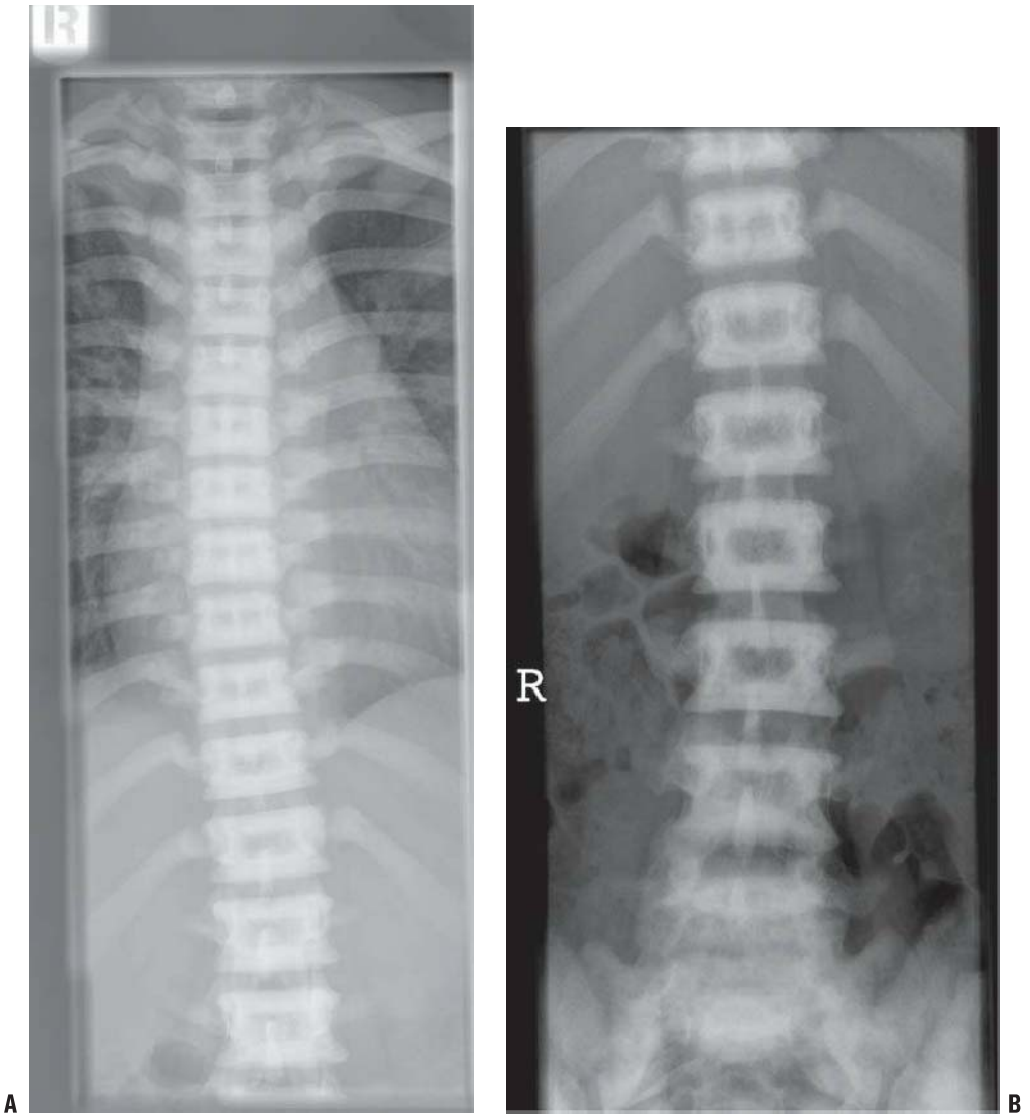
They frequently have infections of the bones or mandibles. Searching nystagmus is described. Patients are pale due to anemia and hepatosplenomegaly due to extramedullary hematopoiesis. A prominent forehead and broad upper skull with hypertelorism are common features.

The milder autosomal dominant adult form of osteopetrosis can present with pathologic fractures and dull pain in people with mild degrees of short stature and prominent forehead. Other people with the autosomal dominant form are so mildly affected that the diagnosis is made incidentally based on the very curious appearance of the bones.

An intermediate clinical type of osteopetrosis is described and includes patients with more severe phenotypes who survive into adulthood. Classifications, which are based on identification of genetic defect, have begun to expand, so that there are at least six types of osteopetrosis based on the genetic aspects, but the genetic classification is not currently comprehensive enough to replace the clinical classification of the disease (301).

The striking radiographic characteristic is that the bones are dense white without medullary cavities and appear marble-like. A bone within bone or endobone appearance can be seen within the pelvis. Marked sclerosis of the end plates of the vertebral bodies can give a rugger–jersey spine appearance (Fig. 6-22). They can be significant sclerosis of the base of the skull. Failure of metaphyseal cutback by osteoclast leads to an Erlenmeyer flask shape of the epiphysis. Secondary deformities including progressive coxa vara or apex lateral bowing of the femur may be present (300, 302, 303).

Etiology. Osteopetrosis is caused by specific osteoclast defects, which prevent the osteoclast from carrying out its normal function in resorbing bone. Many specific defects have been identified. These include carbonic and hydrase deficiency which prevents the osteoclasts from acidifying the extracellular space at the ruffled border. This is associated with the milder clinical forms and can be associated with distal renal tubular



A B

FIGURE 6-22. **A,B:** The classic rugger jersey appearance of the spine is seen in this 15-year-old girl with osteopetrosis.

acidosis and with intercranial calcifications which are unique to this form (304–306). Fatal infantile forms of osteopetrosis have been associated with defects in the genes coding for proton pump or chloride channel protein production (307). More recent case reports describe iatrogenic osteopetrosis as a result of bisphosphonate treatment (188, 308).

All causes of osteopetrosis decrease the function of the osteoclast resorbing of bone. The histologic hallmark is remnants of primary spongiosa within the bone. These are areas of calcified cartilage that are precursor to enchondral bone formation and are normally removed during the first pass remodeling in the fetal life. The ongoing failure to resolve and remodel bone leads to the skeletal manifestations of the diseases, limits the narrow space available and contributes to the pancytopenia and hepatosplenomegaly, and is also responsible for the cranial nerve compression at the skull base. The predisposition toward musculoskeletal infections is thought to be a combination of the abnormal bony architecture and the absence of sufficient white blood cells.

Medical Treatment. Bone marrow transplantation for the severe forms of infantile osteopetrosis was first described in 1977 (309) and this has since been widely reported (310–312). Successful bone marrow transplant corrects both the skeletal and hematologic abnormalities associated with osteopetrosis. However, not all bone marrow transplantations are successful and not all patients have survived. Additional medical treatment can include very high doses of calcitriol to stimulate osteoclastic activity, and the administration of interferon gamma to stimulate superoxide production by osteoclasts. Long-term therapy with interferon gamma in patients with osteopetrosis increases bone resorption and hematopoiesis and improves leukocyte function (313).

Orthopaedic Treatment. Most patients presenting to pediatric orthopaedists do so because of fractures (314). The majority of fractures in children with osteopetrosis will heal well if treated with closed means, although healing can be delayed (Fig. 6-23). The principle exception to this are fractures of the femoral neck and intratrochanteric region, which can be extremely difficult to manage (Fig. 6-24). In Armstrong's survey of the experience of the Pediatric Orthopaedic Society of North America, there was a high incidence of nonunion and varus deformity of the femur if femoral neck intertrochanteric fractures were treated by closed means. The results of early operative treatment of femoral neck and intertrochanteric fractures were good, but technical difficulties of obtaining fixation in the dense bone were noted. Worn out or broken drills and even drivers were reported. Subtrochanteric and femoral shaft fractures did well with both closed and open management. Most tibial fractures were managed closed. Multiple fractures of the tibia were reported in some patients but could be well managed with cast management.

Cervical spine fractures are rare and involve the posterior elements and were treated with immobilization. Lumbar spondylolysis and listhesis have also been described (314, 315) and have responded well to nonoperative treatment in children and adolescents, but occasionally required spinal fusion in adults.

Acquired coxa vara can be treated with proximal femoral valgus osteotomies fix by conventional plates or screws with similar technical difficulties noted to those encountered treating femoral fractures.

Some patients with osteopetrosis get osteoarthritis of the hip and knee during midlife. These can be treated with total knee arthroplasty and total hip arthroplasty, although difficulty with reaming the canal and cutting the bone surfaces has been noted.

Caffey Disease. Caffey disease, or infantile cortical hyperostosis, characteristically presents between the ages of 6 weeks and 6 months. The clinical features are of an irritable child, sometimes with fever and with tender soft-tissue swelling over the affected bone. Radiographically, there is abundant subperiosteal new bone and eventually thickening of the cortex (Fig. 6-25). Episodes are usually self-limiting and may recur episodically, but typically resolves by the age of 2 years and most cases do not require any active orthopaedic treatment. Laboratory investigation can show an increased erythrocyte sedimentation rate (ESR), an increased white blood cell count, an increased alkaline phosphatase and an iron deficiency anemia. Differential diagnosis includes child abuse, infection, and metastatic neoplasms. Caffey was a radiologist who initially described the condition while working on the radiographic presentation of child abuse. A recent linkage analysis has demonstrated a mutation in the COL1A1 gene in patients with Caffey disease (316). This mutation is believed to make the periosteum easily separate from the bone in early infancy, accounting for the typical clinical findings. In addition, older patients in the kindred had voluntary subluxation and hyperextension of joints, suggesting ongoing problems related to the abnormal collagen. Table 6-5 presents a listing of other causes of periosteal reaction and cortical thickening in infancy and early childhood.

Pyknodysostosis. This is similar to osteopetrosis in that it is a manifestation of a failure of bone resorption (Fig.6-26). These patients do not produce cathepsin K which normally degrades bone proteins during bone resorption (317–320). It is inherited as autosomal recessive condition. Patients are mildly short with deformities including pectus excavatum, kyphoscoliosis, an oblique angle of the mandible, failure fusion of the sutures of the skull in adulthood, proptosis, oblique nose, and frontal bossing (321–323). Growth hormone therapy has been used for stature (323). Orthopaedic management is similar to that of osteopetrosis.

Over Production of Bone by Osteoblasts. There are several rare conditions in which osteoblasts overproduce bone because of abnormalities in normal regulation. These conditions are caused by defects in the transforming growth factor beta (TGF β) super family of proteins which are known to regulate bone growth. The three clinical conditions include melorheostosis, Camurati-Engelmann disease, and sclerostenosis.

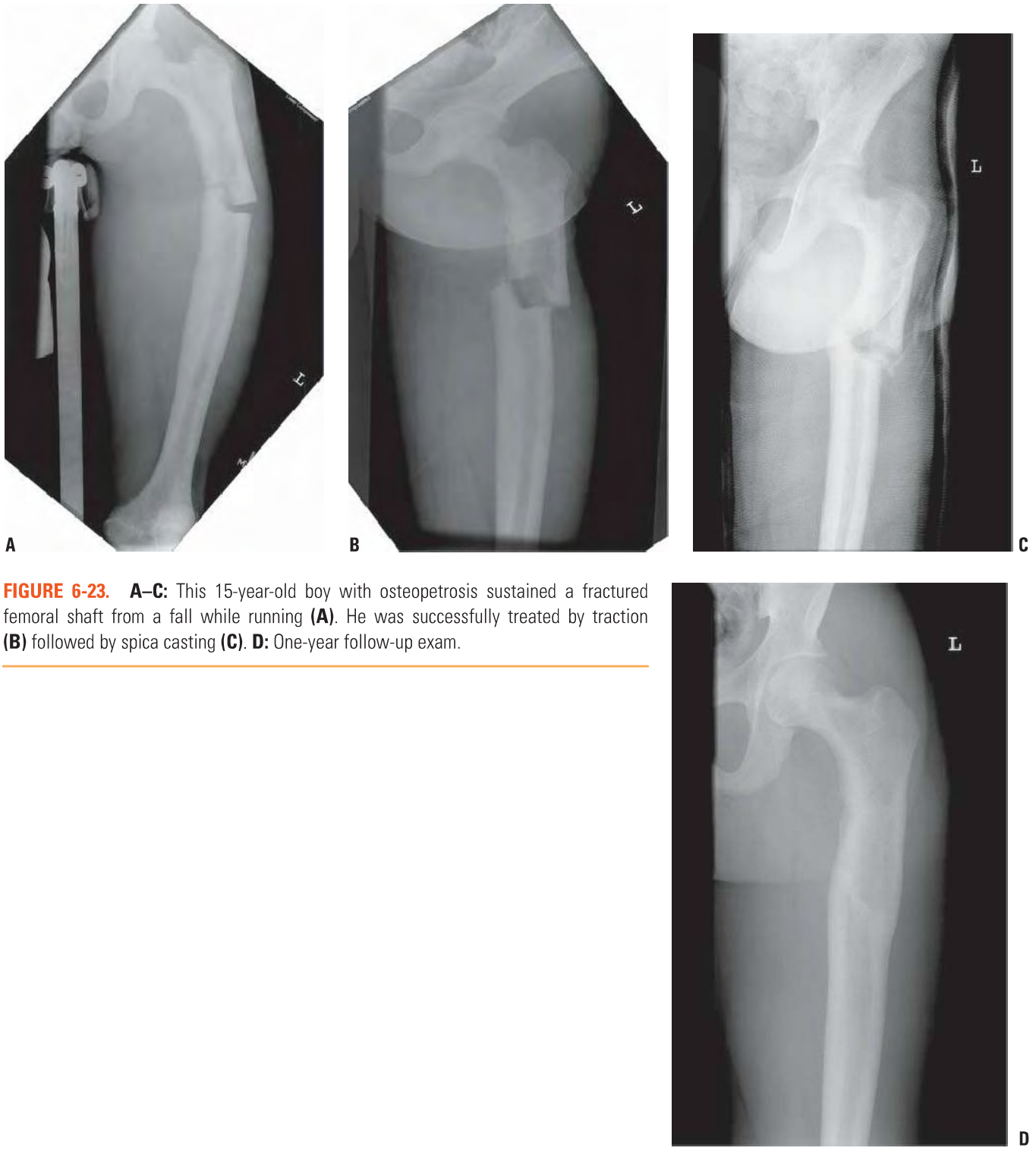


FIGURE 6-23. **A–C:** This 15-year-old boy with osteopetrosis sustained a fractured femoral shaft from a fall while running **(A)**. He was successfully treated by traction **(B)** followed by spica casting **(C)**. **D:** One-year follow-up exam.

Melorheostosis is best remembered by its Greek name which describes flowing wax on a burning candle. The condition is characterized by new periosteal and endosteal bone, which resembles dripping wax radiographically. It typically affects one limb or one side and produces irregularities of cortical bone with a lesion or rash overlying on the skin. The etiology is believed to be downregulation of beta IG-H_3 (324). Somatic mosaicism is thought to explain the usual single limb manifestation (325). There may be stiffness in the soft tissues and shortening or contracture of the affected extremity and the lesion may present with pain (326). Sarcomas arising in melorheostotic lesions have been reported (327–329). Ilizarov treatment has been useful in treating limb shortening and deformity (330, 331), but abnormal bone and soft-tissue–related complications are recorded (332). Soft-tissue contractures are often more problematic for the patient than the bony deformity, but they are difficult to treat operatively with an over 50% recurrence rate, and complications including distal ischemia (326).

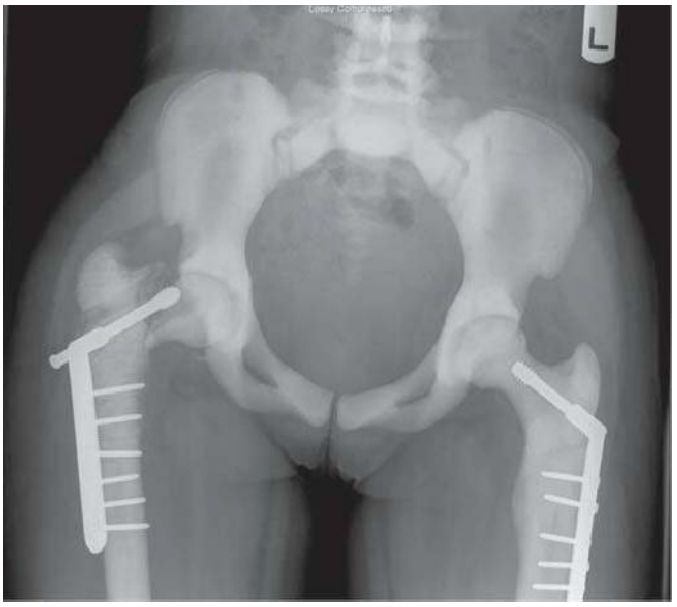


FIGURE 6-24. This 12-year-old girl with osteopetrosis has had bilateral femoral neck fractures treated with open reduction and internal fixation. The left has united but the right has had nonunion and cutout despite revisions of hardware. The bone has been likened to chalk—dense but brittle—leading to a high rate of complications associated with internal fixation.

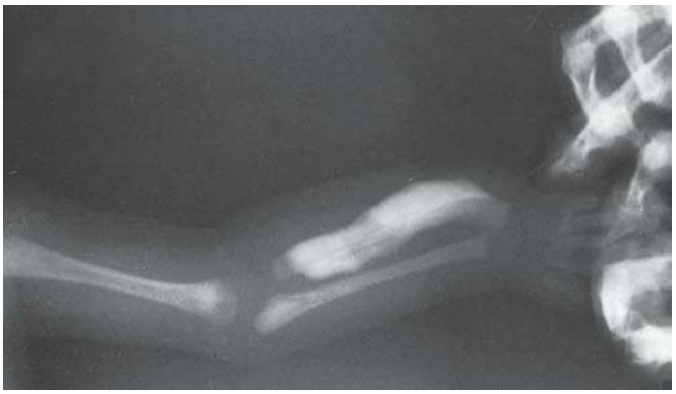


FIGURE 6-25. The ulna is the most frequently affected bone in the extremities of patients with Caffey disease.

TABLE 6-5 Causes of Conditions Associated with Periosteal Reaction and cortical Thickening in Infancy and Early Childhood

Cause	Time of Presentation	Characteristics
Physiologic periosteal reaction of newborn	Age 1–6 mo	Thin, even periosteal reaction symmetric along femora, tibiae, humeri
Congenital or Genetic Condition		
Menkes kinky-hair syndrome	Newborn	Failure to thrive; X-linked defective copper absorption; boys; sparse, kinky hair; central nervous system degeneration, metaphyseal fractures, and periosteal reaction; can be mistaken for abuse or rickets
Camurati-Engelmann (diaphyseal dysplasia)	Age 4–6 yr	Autosomal dominant; progressive midshaft thickening of long bones; waddling gait; normal laboratory findings, except slight elevation of alkaline phosphatase
Infection		
Osteomyelitis	Any age	Classic bacterial osteomyelitis with lytic or blastic changes at metaphysis and periosteal reaction as disease progresses; elevated ESR; viral and fungal types exist; *Salmonella* osteomyelitis in sickle cell disease may begin at diaphysis; ESR not elevated
Congenital syphilis	Age >3 mo (severe spirochetal infection can cause fetal loss)	Many manifestations possible; osteochondritis with metaphyseal lytic lesions; diaphyseal osteitis; periostitis; positive serology for syphilis
Inflammatory Disease		
Juvenile chronic arthritis	Age 5–10 yr	Periarticular reaction at phalanges, metacarpals, and metatarsals
Trauma		
Accidental or nonaccidental injury	Any age	Accidental injury should result in local reaction consistent with age-appropriate activities (i.e., single tibial reaction 7–10 d after injury in a child who is walking); nonaccidental injury can result in multiple areas of periosteal reaction inconsistent with age-appropriate activities

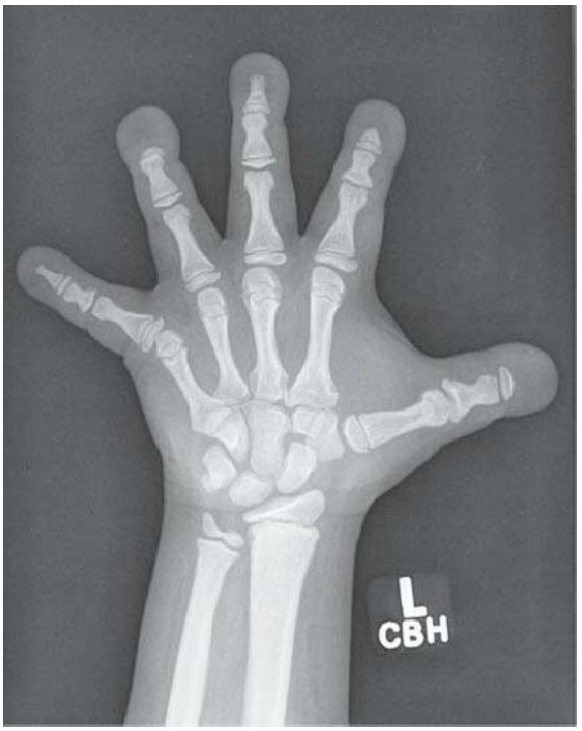


FIGURE 6-26. Pykodysostosis. This 12-year-old boy has the dense bones and acroosteolysis characteristic of pyknodysostosis.

Camurati-Engelmann disease is an autosomal dominant condition that includes hyperostosis, typically with accumulation of the bone within the medullary canal and the diaphyseal region and in the skull. Clinical features include an enlarged head, proptosis, and thin limbs, with weak proximal muscle leading sometimes to a waddling gait and musculoskeletal pain (322, 333). Spontaneous improvement at puberty has been described. Cranial nerve abnormalities and increased intracranial pressure are possible sequelae. The disorder is called by an excess of active TGF beta1 which leads to continuous stimulation of osteoblastic bone deposition (301, 334, 335).

Sclerostenosis is a rare condition inherited in an autosomal recessive pattern (336). It is characterized by skeletal overgrowth particularly of the skull and of the mandible. In addition, patients have sclerotic long bones and gigantism. Bony syndactyly is a characteristic clinical tip off (337–342). Increased intracranial pressure in this condition may lead to sudden death, so recognition of this condition is important (343). The underlying defect is loss of function and mutation in the SOST gene (344, 345). No specific medical treatment is currently available.

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